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(54) **Alkene, alkyne or cycloalkylene derivatives.**

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(56) References cited:  
**EP-A- 0 154 528**  
**FR-A- 2 314 912**  
**US-A- 3 978 097**  
**US-A- 4 139 561**  
**US-A- 4 665 092**

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**CHEMICAL ABSTRACTS, 1970, vol. 72, no.**  
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**CHEMICAL ABSTRACTS, 1986, vol. 104, no.**

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## Description

This invention relates to novel alkene, alkyne or cycloalkylene derivatives which possess antiandrogenic properties.

5 Various 4-arylbut-3-en-2-ol derivatives of the general formula:-



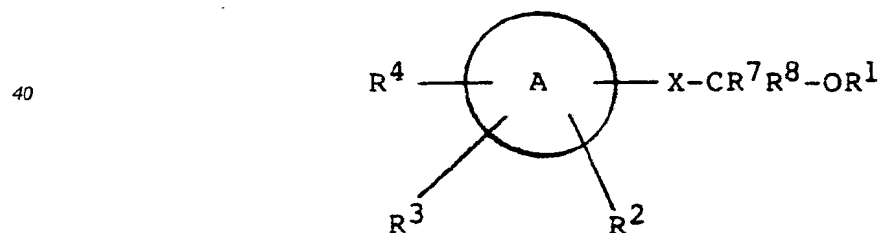
wherein Ar is a phenyl group bearing one or more electron-withdrawing substituents, are known, for a variety of purposes. For example, such compounds wherein R<sup>7</sup> is t-butyl and R<sup>8</sup> is imidazol-1-ylmethyl or 1,2,4-triazol-1-ylmethyl are known, from European Patent Specifications Nos 40345 and 52424 and other related specifications, as plant growth regulators or fungicides. When R<sup>7</sup> and R<sup>8</sup> are both methyl the compound wherein Ar is 3-nitrophenyl is known from United States Patent specification No. 4139561, and the compound wherein Ar is 4-chlorophenyl is known from Synthesis, 1980, pages 815-816, in both cases the compounds being used as chemical intermediates. When R<sup>7</sup> is methyl, R<sup>8</sup> is carboxymethyl or ethoxycarbonylmethyl and Ar is 4-chlorophenyl, the compounds are described in Biochemistry, 1964, Volume 3, pages 1998 et seq., as potential (although inactive) inhibitors of cholesterol biosynthesis.

Various acylanilides of the general formula



30 are known as antiandrogens. The compounds wherein R<sup>7</sup> and R<sup>8</sup> are both methyl and Ar is 4-nitro-3-trifluorophenyl is known as hydroxyflutamide, and is believed to be the active metabolite of the commercially-available antiandrogen FLUTAMIDE. Other acylanilides which possess antiandrogenic activity are known from European Specifications Nos 2309, 2892 and 40932, and from Japanese Specification No. 52-128329.

35 According to the present invention there is provided a compound of the formula



45 wherein X has the formula or



55 wherein ring A is phenyl, naphthyl or heterocyclic;

wherein R<sup>1</sup> is hydrogen, alkyl or alkanoyl each of up to 6 carbon atoms or aroyl of up to 10 carbon atoms;  
 wherein R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup>, which may be the same or different, each is an electron withdrawing substituent  
 selected from halogeno, nitro, cyano and trifluoromethyl, and alkylthio, alkylsulphinyl and alkylsulphonyl  
 each of up to 6 carbon atoms, or each is hydrogen or alkyl, alkoxy or dialkylamino each of up to 6 carbon  
 5 atoms, provided that when ring A is phenyl or naphthyl at least one of R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> is an electron-  
 withdrawing substituent;  
 wherein R<sup>5</sup> and R<sup>6</sup>, which may be the same or different, each is hydrogen, halogeno or alkyl of up to 6  
 carbon atoms, ;  
 wherein R<sup>7</sup> is alkyl or halogenoalkyl each of up to 6 carbon atoms;  
 10 and wherein R<sup>8</sup> has the formula



wherein Y is straight- or branched-chain alkylene or alkenylene each of up to 6 carbon atoms;  
 15 wherein Q is -O-, -S-, -SO- or -SO<sub>2</sub>-;  
 and wherein R<sup>9</sup> is alkyl of up to 6 carbon atoms which contains one or more substituents selected from  
 halogeno, cyano, hydroxy, amino, hydroxyimino, guanidino, ureido and carbamoyl;  
 alkoxy, alkylamino, alkylthio, alkylsulphinyl, alkylsulphonyl, alkylcarbamoyl, alkoxyimino, alkanoyl,  
 halogenoalkanoyl, alkanoylamino and alkylsulphonamido each of up to 6 carbon atoms;  
 20 alkoxyalkoxy, dialkylamino and dialkylcarbamoyl each of up to 12 carbon atoms;  
 aryl, aryloxy, arylthio, arylsulphinyl, arylsulphonyl, aryloxyimino and aroyl each of up to 10 carbon atoms;  
 heterocyclyl, heterocyclylthio, heterocyclylsulphinyl, heterocyclylsulphonyl, heterocyclyloxyimino and  
 heterocyclylcarbonyl;  
 and alkyleneedioxy of to 2 to 4 carbon atoms wherein both oxygen atoms are attached to the same carbon  
 25 atom of R<sup>9</sup>.

It will be observed that a compound of the invention wherein x is other than ethynylene may exist in two  
 geometrical isomeric forms depending upon the disposition of the various substituents about the olefinic or  
 cycloalkyl bond -X-, and also that a compound of the invention possesses at least one asymmetric carbon  
 atom, namely the carbon atom which bears the substituents R<sup>7</sup>, R<sup>8</sup> and -OR<sup>1</sup>, and it can therefore exist in  
 30 racemic and optically-active forms. It is to be understood that this invention encompasses either geometric  
 isomer in racemic form, and any optically-active form of the compound which possesses antiandrogenic  
 activity, it being a matter of common general knowledge how a racemic compound may be resolved into its  
 optically-active forms and how any antiandrogenic activity present in any of these forms may be  
 determined.

35 A suitable value for ring A when it is heterocyclyl, or for the heterocyclyl, heterocyclylthio-, sulphinyl- or  
 sulphonyl-, heterocyclyloxyimino or heterocyclylcarbonyl substituent in R<sup>9</sup> is, for example, a 5- or 6-  
 membered saturated or unsaturated heterocyclic which contains one, two or three hetero atoms selected  
 from oxygen, nitrogen and sulphur, which heterocyclic is a single ring or is fused to one or two benzo-rings  
 or to another heterocyclic ring as defined above, and which heterocyclic is unsubstituted or bears  
 40 substituents R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> as defined above, or when a substituent in R<sup>9</sup> may also bear one or more  
 hydroxy, mercapto or amino substituents.

Ring A when heterocyclic is preferably pyridyl, quinolyl or thienyl which is unsubstituted or bears one  
 or two halogeno or cyano substituents, or one nitro substituent.

When R<sup>9</sup> is alkyl bearing a heterocyclyl containing substituent the heterocyclyl group is preferably furyl,  
 45 thienyl, pyridyl, quinolyl, pyrimidinyl, pyrazinyl, thiazolyl, imidazolyl, triazolyl, purinyl, 1,4-benzodioxanyl,  
 pyrazolopyrimidinyl or acridinyl which is unsubstituted or bears one or more substituents selected from  
 halogeno, trifluoromethyl, hydroxy, mercapto and amino, and alkyl and alkoxy each of up to 6 carbon  
 atoms.

A suitable value for R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup> or R<sup>7</sup> when it is alkyl is, for example, methyl, ethyl, n-propyl,  
 50 isopropyl, n-butyl or n-hexyl.

A suitable value for R<sup>1</sup> when it is alkanoyl, or for the alkanoyl substituent in R<sup>9</sup> when R<sup>9</sup> is alkyl  
 substituted by alkanoyl is, for example, formyl, acetyl or propionyl.

A suitable value for R<sup>1</sup> when it is aroyl, or for the aroyl substituent in R<sup>9</sup> when R<sup>9</sup> is alkyl substituted by  
 aroyl, is, for example, benzoyl, p-fluorobenzoyl or p-toluoyl.

55 A suitable value for R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup> or R<sup>6</sup> when it is halogeno, or for the halogeno substituent in R<sup>7</sup> or R<sup>9</sup>  
 is, for example, fluoro, chloro or bromo.

A suitable value for R<sup>2</sup>, R<sup>3</sup> or R<sup>4</sup> when it is alkoxy, or for the alkoxy substituent in R<sup>9</sup> when R<sup>9</sup> is alkyl  
 substituted by alkoxy is, for example, methoxy or ethoxy.

A suitable value for R<sup>2</sup>, R<sup>3</sup> or R<sup>4</sup> when it is alkylthio, alkylsulphinyl or alkylsulphonyl, or for the alkylthio, alkylsulphinyl or alkylsulphonyl substituent in R<sup>9</sup> when R<sup>9</sup> is alkyl substituted by alkylthio, alkylsulphinyl or alkylsulphonyl is, for example, methylthio, ethylthio, n-propylthio, methylsulphinyl, ethylsulphinyl, n-propylsulphinyl, methylsulphonyl, ethylsulphonyl or n-propylsulphonyl.

5 A suitable value for R<sup>2</sup>, R<sup>3</sup> or R<sup>4</sup> when it is dialkylamino, or for the dialkylamino substituent in R<sup>9</sup> when R<sup>9</sup> is alkyl substituted by dialkylamino is, for example, dimethylamino or diethylamino.

A suitable value for R<sup>7</sup> when it is halogenoalkyl is, for example, trifluoromethyl, pentafluoroethyl, heptafluoropropyl, chloromethyl or dichloromethyl.

10 A suitable value for the alkanoylamino, alkylsulphonamido, alkylamino, alkylcarbamoyl, dialkylcarbamoyl, alkoxyimino, halogenoalkanoyl or alkoxyalkoxy substituent in R<sup>9</sup> when R<sup>9</sup> is alkyl which bears such a substituent is, for example, acetamido, methylsulphonamido, methylamino, ethylamino, methylcarbamoyl, dimethylcarbamoyl, methoxyimino, chloroacetyl or methoxyethoxy.

15 A suitable value for the aryl, aryloxy, arylthio, arylsulphinyl, arylsulphonyl or aryloxyimino substituent in R<sup>9</sup> when R<sup>9</sup> is alkyl which bears such a substituent is, for example, phenyl, naphthyl, tolyl, fluorophenyl, chlorophenyl, methoxyphenyl, nitrophenyl, methylthiophenyl, methylsulphonylphenyl, carbamoylphenyl, acetamidophenyl or dimethylaminophenyl, or the corresponding phenoxy, phenylthio, phenylsulphinyl, phenylsulphonyl, phenoxyimino or substituted phenoxy, phenylthio, phenylsulphinyl, phenylsulphonyl or phenox-

20 A preferred compound of the invention has the formula stated above wherein X is -CR<sup>5</sup>=CR<sup>6</sup>-, in the trans- configuration, wherein ring A is phenyl, wherein one or two (the same or different) of R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are fluoro, chloro, cyano, trifluoromethyl or nitro, the others of R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> being hydrogen, wherein R<sup>1</sup>, R<sup>5</sup> and R<sup>6</sup> are all hydrogen, wherein R<sup>7</sup> is trifluoromethyl, pentafluoroethyl, heptafluoropropyl, chloromethyl or dichloromethyl; wherein Q is -S-, -SO- or -SO<sub>2</sub>-, wherein Y is -CH<sub>2</sub>- and wherein R<sup>9</sup> is straight-chain-alkyl of up to 4 carbon atoms which bears one or two substituents selected from chloro, cyano, hydroxy, amino, 25 carbamoyl, methoxy, ethoxy, methylthio, methylsulphonyl, acetyl, acetamido, ureido, dimethylamino, dimethylcarbamoyl, phenyl, fluorophenyl, methylthiophenyl, methylsulphonylphenyl, naphthyl, methoxyphenoxy, phenylthio, methylthiophenylthio, methylsulphonylphenylthio, benzoyl, thenoyl, furyl, pyridyl, pyrazinyl, methylthiazolyl and 1,4-benzodioxanyl; or which bears one such substituent and also three fluorine substituents on the terminal carbon atom; or which bears an ethylenedioxy or trimethylene-1,3-dioxy 30 substituent; or which bears three fluorine substituents on the terminal carbon atom.

A particularly preferred compound of the invention is one defined in the last paragraph above wherein ring A is 3,4-dichlorophenyl, 3-chloro-4-cyanophenyl, 4-cyano-3-trifluoromethylphenyl or 4-fluoro-3-trifluoromethylphenyl and wherein R<sup>7</sup> is trifluoromethyl.

35 Specific compounds of the invention are hereinafter described in the Examples. Of these, preferred compounds by virtue of their high level of antiandrogenic activity are:-

1-(3-methoxypropylthio)-, 1-(3-hydroxybutylthio)-, 1-(2-hydroxypropylthio)-, 1-[3,3-(trimethylene-1,3-dioxy)-propylthio]-, 1-(2-furylmethylthio)-, 1-(3-oxobutylthio)-, 1-(3,3-ethylenedioxybutylthio)-, 1-(3-hydroxypropylthio)-, 1-(2,3-dihydroxypropylthio)-, 1-(2,3-dimethoxypropylthio)-, 1-benzylthio-, 1-(3-phenylpropylthio)-, 1-m-fluorobenzylthio-, 1-p-fluorobenzylthio-, 1-(3-p-methoxyphenylpropylthio)-, 1-(2-carbamoylethylthio)-, 1-(2-N,N-dimethylcarbamoylethylthio)-, 1-(pyrid-3-ylmethylthio)-, 1-(2-methylthiazol-4-ylmethylthio)-, 1-(3-phenoxypropylthio)-, 1-(4-oxo-4-phenylbutylthio)-, 1-[4-oxo-4-(thien-2-yl)butylthio]-, 1-(3-hydroxy-3-phenylpropylthio)-, 1-(3-p-fluorophenyl-3-hydroxypropylthio)-, 1-(3-hydroxy-3-p-methylthiophenylpropylthio)-, 1-(3-hydroxy-3-p-methylsulphonylphenylpropylthio)- and 1-(3-hydroxy-3-p-methoxyphenylpropylthio)-4-(4-cyano-3-trifluoromethylphenyl)-2-trifluoromethylbut-trans-3-en-2-ol;

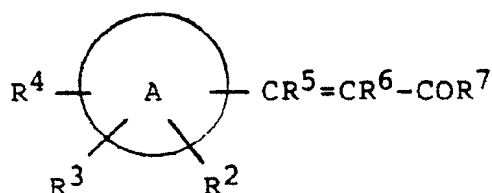
45 1-(2-carbamoylethylthio)-, 1-(p-methylsulphonylbenzylthio)- and 1-(3-methoxypropylthio)-4-(3-chloro-4-cyanophenyl)-2-trifluoromethylbut-trans-3-en-2-ol; and

1-(3-methylsulphonylpropylsulphonyl)-4-(3,4-dichlorophenyl)-2-trifluoromethylbut-trans-3-en-2-ol.

A compound of the invention may be manufactured by any chemical process known to be suitable for the manufacture of chemically-analogous compounds.

50 One process for the manufacture of an alkene of the invention wherein R<sup>1</sup> is hydroxy and X is -CR<sup>5</sup>=CR<sup>6</sup>- comprises the reaction of a compound of the formula:

5

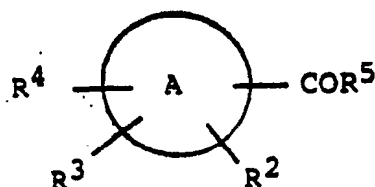


10 wherein A, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup> and R<sup>7</sup> have the meanings stated above, with an organometallic compound of the formula R<sup>8</sup>-M, wherein R<sup>8</sup> has the meaning stated above and M is a metallic group.

M may be, for example, lithium, and the reaction is preferably carried out in an inert diluent or solvent, for example tetrahydrofuran, at a reduced temperature, for example at -70 °C to -80 °C.

15 The starting material for the abovementioned reaction may be obtained by the reaction of an aldehyde or ketone of the formula:

20



25 wherein A, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> have the meanings stated above, with a compound of the formula R<sup>5</sup>CH<sub>2</sub>COR<sup>7</sup> or (Ph)<sub>3</sub>P=CR<sup>6</sup>COR<sup>7</sup> or

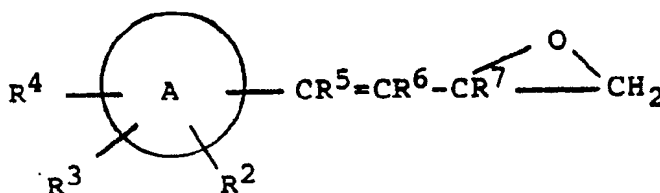
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wherein R<sup>6</sup> and R<sup>7</sup> have the meanings stated above.

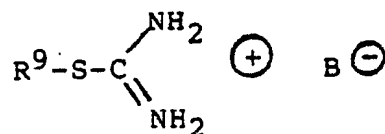
35 An alternative process for the manufacture of an alkene of the invention wherein R<sup>1</sup> is hydroxy, X is -CR<sup>5</sup>=CR<sup>6</sup>-, and Y is -CH<sub>2</sub>- comprises the reaction of an epoxide of the formula:

40



45 wherein A, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup> and R<sup>7</sup> have the meanings stated above, with a compound of the formula R<sup>9</sup>-Q-H, wherein R<sup>9</sup> and Q have the meanings stated above or, when Q is -S-, with the corresponding isothiuronium salt of the formula

50



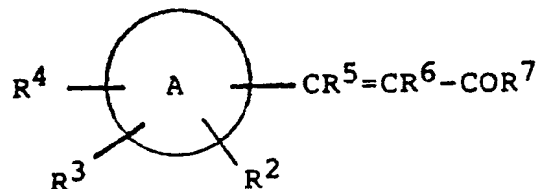
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wherein B<sup>⊖</sup> is an anion, for example the chloride, bromide or tosylate ion.

The abovementioned reaction is particularly suitable for the manufacture of an alkene of the invention wherein Q is -S- or wherein the -H atom is otherwise reactive. The reaction is conveniently carried out at

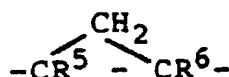
laboratory temperature in an inert diluent or solvent, for example tetrahydrofuran or diethyl ether, or, when an isothiuronium salt is used in tetrahydrofuran in the presence of an aqueous base, for example sodium hydroxide solution.

The epoxide starting material may be obtained by the reaction of a compound of the formula:

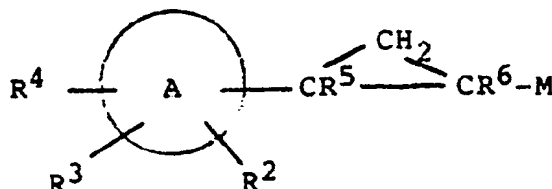


(the preparation of which is described above) with trimethylsulphoxonium iodide in the presence of a base, for example butyl-lithium or, under phase transfer conditions, an alkali metal hydroxide.

A process for the manufacture of a cycloalkylene derivative of the invention wherein X is



comprises the reaction of a compound of the formula



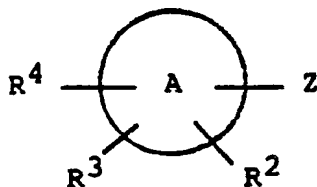
wherein A, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup> and M have the meanings stated above, with a compound of the formula



wherein R<sup>7</sup> and R<sup>8</sup> have the meanings stated above.

This reaction may be carried out at a low temperature in an inert diluent or solvent. M is preferably lithium.

A process for the manufacture of an alkyne of the invention wherein X is -C≡C- comprises the reaction of a compound of the formula



wherein A, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> have the meanings stated above and wherein Z is a displaceable group, with a compound of the formula



wherein R<sup>1</sup>, R<sup>7</sup> and R<sup>8</sup> have the meanings stated above.

A suitable value for Z is, for example, an iodo group.

A compound of the invention wherein X is  $\text{-C}\equiv\text{C-}$  may be reduced to the corresponding compound of the invention wherein X is  $\text{-CH=CH-}$ . Conventional conditions for the reduction may be chosen so that either the cis- or trans- alkene is obtained.

5 Various interconversions of compounds of the invention wherein  $\text{R}^9$  has different meanings are possible. Thus, for example

(i) a compound wherein  $\text{R}^9$  bears an amino substituent may be acylated to give the corresponding compound wherein  $\text{R}^9$  bears an alkanoylamino, alkoxycarbonylamino or alkylsulphonamido substituent;

(ii) a compound wherein  $\text{R}^9$  is alkyl substituted by alkanoyl may be reduced to the corresponding  
10 compound wherein  $\text{R}^9$  is hydroxyalkyl.

A compound of the invention wherein  $\text{R}^1$  is alkyl may be prepared by the alkylation of the corresponding compound wherein  $\text{R}^1$  is hydrogen.

A compound of the invention wherein  $\text{R}^1$  is alkanoyl or aroyl may be prepared by the acylation of the corresponding compound wherein  $\text{R}^1$  is hydrogen.

15 A compound of the invention wherein one or more of  $\text{R}^2$ ,  $\text{R}^3$ ,  $\text{R}^4$  and a substituent in  $\text{R}^9$  is alkylsulphinyl or alkylsulphonyl, or a substituent in  $\text{R}^9$  is arylsulphinyl, arylsulphonyl, heterocyclsulphinyl or heterocyclsulphonyl, or Q is  $\text{-SO-}$  or  $\text{-SO}_2\text{-}$ , may be prepared by the oxidation of the corresponding compound wherein one or more of  $\text{R}^2$ ,  $\text{R}^3$ ,  $\text{R}^4$  and a substituent in  $\text{R}^9$  is alkylthio, arylthio or heterocyclthio, or Q is  $\text{-S-}$ , respectively. The oxidising agent and conditions used will determine whether a sulphinyl or a sulphonyl  
20 compound is obtained. Thus, oxidation with sodium metaperiodate in methanol solution at or below laboratory temperature will generally convert a thio compound into the corresponding sulphinyl compound; and oxidation with hydrogen peroxide in acetic acid solution or with a persulphate in aqueous solution at or above laboratory temperature, will generally convert a thio compound into the corresponding sulphonyl compound, although this reaction occasionally stops at the sulphinyl stage.

25 As stated above, a compound of the invention possesses antiandrogenic properties as demonstrated by its ability to decrease the weight of the seminal vesicles of a castrated male rat when administered concurrently with testosterone propionate. A compound of the invention may therefore be used in the treatment of, for example, malignant or benign prostatic disease or of androgen dependent disease conditions, such as acne, hirsutism or seborrhoea, in warm-blooded vertebrates including man. It may also  
30 be used to improve ovulation in a domestic animal.

At a dose of a compound of the invention which produces antiandrogenic activity in rats no symptom of toxicity is apparent.

The compound of the invention may be administered to a warm-blooded animal in the form of a pharmaceutical or veterinary composition which comprises the compound in association with a  
35 pharmaceutically-acceptable diluent or carrier.

The composition may be in a form suitable for oral dosage, as a tablet, capsule, aqueous or oily solution or suspension, or emulsion. It may alternatively be in the form of a sterile solution or suspension suitable for parenteral administration, or be in the form of an ointment or lotion for topical administration, or be in the form of a suppository.

40 The composition may additionally contain one or more drugs selected from anti-oestrogens, for example tamoxifen; aromatase inhibitors, for example testolactone or aminoglutethimide; progestins, for example medroxyprogesterone acetate; inhibitors of gonadotrophin secretion, for example danazol; LH-RH analogues, for example buserelin; cytotoxic agents, for example cyclophosphamide; antibiotics, for example penicillin or oxytetracyclin; and anti-inflammatory agents, for example, especially for topical use,  
45 fluocinolone acetonide.

The compound of the invention will normally be administered to a warm-blooded animal at a dose of between 0.1 mg. and 125 mg. per kg. bodyweight.

The invention is illustrated but not limited by the following Examples:-

#### 50 Example 1

A solution of 4-(3,4-dichlorophenyl)-1,2-epoxy-2-trifluoromethylbut-trans-3-ene (0.3 g.) in tetrahydrofuran (5 ml.) was added dropwise to a stirred mixture of 2-methylthioethanethiol (0.2 g.) and sodium hydride (0.08 g. of a 50% dispersion in mineral oil) in tetrahydrofuran (25 ml.) and the mixture was stirred at laboratory  
55 temperature for 1.5 hours and then poured into water. The mixture was extracted with ethyl acetate and the extract was washed with saturated aqueous sodium chloride solution, dried over magnesium sulphate and evaporated to dryness under reduced pressure. The residue was purified by chromatography on a silica gel column using a 3:2 v/v mixture of petroleum ether (b.p. 60-80 °C.) and methylene chloride as eluant. There

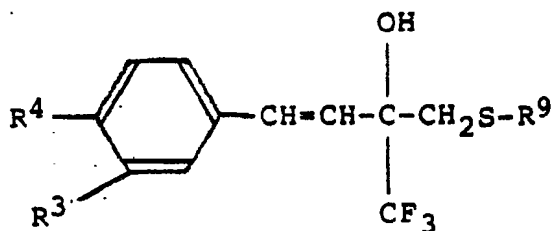
was thus obtained as an oil 4-(3,4-dichlorophenyl)-1-[(2-methylthioethyl)thio]-2-trifluoromethylbut-trans-3-en-2-ol, m.p. 64 °C.

The epoxybutene used as starting material was obtained as follows:-

A solution of 3,4-dichlorobenzaldehyde (10 g.) in ethanol (50 ml.), and then 1,1,1-trifluoroacetone (6.5 ml.), were successively added to a stirred suspension of freshly ground lithium hydroxide monohydrate (1.0 g.) in ethanol (100 ml.), the trifluoroacetone being added by injection below the surface of the reaction mixture, and the mixture was stirred for 1 hour and then poured into water (600 ml.). The mixture was extracted with ethyl acetate and the extract was washed with aqueous 2N-hydrochloric acid and then saturated aqueous sodium chloride solution, dried over magnesium sulphate and evaporated to dryness under reduced pressure. The residue was purified by chromatography on a silica gel column using a 7:3 v/v mixture of petroleum ether (b.p. 60-80 °C.) and methylene chloride as eluant. There was thus obtained 1,1,1-trifluoro-4-(3,4-dichlorophenyl)but-trans-3-en-2-one, m.p. 81 °C.

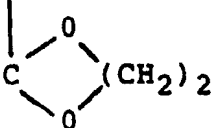
n-Butyl-lithium (11.6 ml. of a 1.6 molar solution in hexane) was added dropwise to a stirred suspension of trimethylsulphoxonium iodide (4.1 g.) in tetrahydrofuran (200 ml.) which was cooled to -10 °C., and the mixture was stirred at that temperature for 2 hours and then added to a stirred solution of 4-(3,4-dichlorophenyl)-1,1,1-trifluorobut-trans-3-en-2-one (2.0 g.) in tetrahydrofuran (100 ml.). The mixture was stirred for 90 minutes, saturated aqueous ammonium chloride solution (75 ml.) was added and the mixture was partitioned between water and ethyl acetate. The layers were separated, the aqueous layer was extracted with ethyl acetate and the combined ethyl acetate solutions were washed with saturated aqueous sodium chloride solution, dried over magnesium sulphate and evaporated to dryness under reduced pressure. The residue was purified by chromatography on a silica gel column using a 4:1 v/v mixture of petroleum ether (b.p. 60-80 °C.) and methylene chloride as eluant. There was thus obtained as an oil 4-(3,4-dichlorophenyl)-1,2-epoxy-2-trifluoromethyl-but-trans-3 ene.

The process described above was repeated using the appropriate thiol and the appropriate epoxide, prepared from the appropriate butenone either as described above or by the method generally described in Angewandte Chemie (International Edition), 1973, volume 12, page 845. There were thus obtained the compounds described in the following table:-





	R <sup>3</sup>	R <sup>4</sup>	R <sup>9</sup>	m.p. (°C.)	Note
5	Cl	Cl	CH <sub>2</sub> CHOHCH <sub>2</sub> OH	(oil)	
	CF <sub>3</sub>	CN	CH <sub>2</sub> CHOHCH <sub>2</sub> OH	(oil)	1
	Cl	Cl	(CH <sub>2</sub> ) <sub>2</sub> CHOHCH <sub>3</sub>	(oil)	
10	CF <sub>3</sub>	CN	(CH <sub>2</sub> ) <sub>2</sub> CHOHCH <sub>3</sub>	(oil)	1
	Cl	Cl	(CH <sub>2</sub> ) <sub>2</sub> OH	112-113	
	CF <sub>3</sub>	CN	(CH <sub>2</sub> ) <sub>2</sub> OH	(oil)	1
	Cl	Cl	CH <sub>2</sub> CHOHCF <sub>3</sub>	(oil)	
15	CF <sub>3</sub>	CN	CH <sub>2</sub> CHOHCF <sub>3</sub>	(oil)	1
	Cl	Cl	CH <sub>2</sub> CHOHCH <sub>3</sub>	(oil)	
	CF <sub>3</sub>	CN	CH <sub>2</sub> CHOHCH <sub>3</sub>	(oil)	1
20	CF <sub>3</sub>	CN	$  \begin{array}{c}  \text{O} \\  \diagup \quad \diagdown \\  (\text{CH}_2)_2\text{CH} \quad (\text{CH}_2)_3 \\  \diagdown \quad \diagup \\  \text{O}  \end{array}  $	(oil)	1
25	Cl	Cl	$  \begin{array}{c}  \text{O} \\  \diagup \quad \diagdown \\  (\text{CH}_2)_2\text{C}(\text{CH}_3) \quad (\text{CH}_2)_2 \\  \diagdown \quad \diagup \\  \text{O}  \end{array}  $	(oil)	
30	CF <sub>3</sub>	CN	$  \begin{array}{c}  \text{O} \\  \diagup \quad \diagdown \\  (\text{CH}_2)_2\text{C}(\text{CH}_3) \quad (\text{CH}_2)_2 \\  \diagdown \quad \diagup \\  \text{O}  \end{array}  $	(oil)	1
	CF <sub>3</sub>	CN	(CH <sub>2</sub> ) <sub>2</sub> COCH <sub>3</sub>	(oil)	1
	Cl	Cl	(CH <sub>2</sub> ) <sub>2</sub> COCH <sub>3</sub>	(oil)	
35	Cl	Cl	(CH <sub>2</sub> ) <sub>2</sub> CONH <sub>2</sub>	76	
	Cl	CN	(CH <sub>2</sub> ) <sub>2</sub> CONH <sub>2</sub>	(oil)	1
	CF <sub>3</sub>	CN	(CH <sub>2</sub> ) <sub>2</sub> CONH <sub>2</sub>	(oil)	1
	Cl	CN	(CH <sub>2</sub> ) <sub>2</sub> OCH <sub>3</sub>	54-55	1
40	Cl	Cl	(CH <sub>2</sub> ) <sub>2</sub> N(CH <sub>3</sub> ) <sub>2</sub>	(oil)	
	Cl	CN	(CH <sub>2</sub> ) <sub>2</sub> SCH <sub>3</sub>	(oil)	1
	Cl	Cl	(CH <sub>2</sub> ) <sub>3</sub> SCH <sub>3</sub>	(oil)	
	Cl	CN	(CH <sub>2</sub> ) <sub>3</sub> SCH <sub>3</sub>	(oil)	1
45	CF <sub>3</sub>	CN	(CH <sub>2</sub> ) <sub>3</sub> SCH <sub>3</sub>	(oil)	1
	Cl	CN	(CH <sub>2</sub> ) <sub>2</sub> NHCOCH <sub>3</sub>	(oil)	1
	Cl	Cl	(CH <sub>2</sub> ) <sub>2</sub> NHCONH <sub>2</sub>	118-130	
50	Cl	Cl	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	(oil)	

	R <sup>3</sup>	R <sup>4</sup>	R <sup>9</sup>	m.p. (°C.)	Note
5					
	CF <sub>3</sub>	CN	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	80-84	
	Cl	Cl	(CH <sub>2</sub> ) <sub>2</sub> -4-fluorophenyl	(oil)	
10	Cl	Cl	CH <sub>2</sub> -1-naphthyl	(oil)	
	Cl	Cl	CH <sub>2</sub> -2-furyl	(oil)	
	CF <sub>3</sub>	CN	CH <sub>2</sub> -2-furyl	(oil)	1
	Cl	Cl	(CH <sub>2</sub> ) <sub>2</sub> NH <sub>2</sub>	137-138	
15	Cl	Cl	(CH <sub>2</sub> ) <sub>2</sub> -2-pyrazinyl	(oil)	
	CF <sub>3</sub>	CN	(CH <sub>2</sub> ) <sub>2</sub> -2-pyrazinyl	(oil)	1
	CF <sub>3</sub>	CN	(CH <sub>2</sub> ) <sub>3</sub> O-4-methoxyphenyl	(oil)	1
20	CF <sub>3</sub>	CN	(CH <sub>2</sub> ) <sub>2</sub> CON(CH <sub>3</sub> ) <sub>2</sub>	(oil)	1
	CF <sub>3</sub>	CN	(CH <sub>2</sub> ) <sub>3</sub> CON(CH <sub>3</sub> ) <sub>2</sub>	(oil)	1
	CF <sub>3</sub>	CN	(CH <sub>2</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	58-60	1
25	CF <sub>3</sub>	CN	(CH <sub>2</sub> ) <sub>2</sub> -4-methylthiophenyl	(oil)	1
	CF <sub>3</sub>	CN	CH <sub>2</sub> -2-pyridyl	(oil)	1
	CF <sub>3</sub>	CN	(CH <sub>2</sub> ) <sub>2</sub> -2-pyridyl	(oil)	1
30	CF <sub>3</sub>	CN	CH <sub>2</sub> -(1,4-benzodioxan-2-yl)	(oil)	1
	CF <sub>3</sub>	CN	CH <sub>2</sub> CHOHC <sub>6</sub> H <sub>5</sub>	(oil)	1
35	CF <sub>3</sub>	CN	CH <sub>2</sub> CHOH-4-methylsulphonylphenyl	(oil)	1
	CF <sub>3</sub>	CN	CH <sub>2</sub> CHOH-3-pyridyl	(oil)	1
			4-fluorophenyl		
40	CF <sub>3</sub>	CN		(oil)	1
45	CF <sub>3</sub>	CN	(CH <sub>2</sub> ) <sub>2</sub> CO-4-fluorophenyl	(oil)	2

50 Note 1 The butenone starting material was obtained by the reaction of the appropriate aldehyde with diethyl 3,3,3-trifluoro-2-methyliminopropylphosphonate by the method described in Tetrahedron Letters (1983), page 4229. 4-(4-Cyano-3-trifluoromethylphenyl)-1,1,1-trifluorobut-3-en-2-one has m.p. 119-121° C. and 4-(3-chloro-4-cyanophenyl)-1,1,1-trifluorobut-3-en-2-one has m.p. 102-104° C.

Note 2 Prepared by acid hydrolysis of the preceding compound.

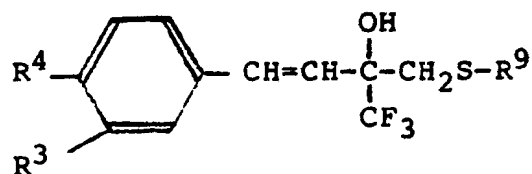
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#### Example 2

A solution of sodium hydroxide (0.06 g.) in water (0.5 ml.) was added dropwise to a stirred suspension

of 3-hydroxy-3-phenylpropylisothiuronium chloride (0.18 g.) in tetrahydrofuran which was maintained at laboratory temperature under an atmosphere of argon, and the mixture was stirred for 15 minutes. A solution of 4-(4-cyano-3-trifluoromethylphenyl)-1,2-epoxy-2-trifluoromethylbut-trans-3-ene (0.205 g.) in tetrahydrofuran (2 ml.) was added and the mixture was stirred at laboratory temperature for 20 hours, diluted with ethyl acetate (20 ml.) and washed with saturated aqueous sodium chloride solution (15 ml.). The organic solution was dried over magnesium sulphate and evaporated to dryness and the residue was purified by flash chromatography on a silica gel (Merck 9385) column using a 2:1 v/v mixture of petroleum ether (b.p. 60-80° C.) and ethyl acetate as eluent. There was thus obtained, as an oil, 4-(4-cyano-3-trifluoromethylphenyl)-1-(3-hydroxy-3-phenylpropyl)thio-2-trifluoromethylbut-trans-3-en-2-ol.

The process described above was repeated using the appropriate isothiuronium chloride (or bromide indicated by an asterisk \* in the table, or tosylate, indicated by two asterisks \*\* in the table) and the appropriate epoxide as starting materials and there were thus obtained the compounds described in the following table:-



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R <sup>3</sup>	R <sup>4</sup>	R <sup>9</sup>	m.p. (°C.)
Cl	Cl	(CH <sub>2</sub> ) <sub>3</sub> CF <sub>3</sub>	(oil)
Cl	CN	(CH <sub>2</sub> ) <sub>3</sub> CF <sub>3</sub>	(oil)
Cl	Cl	(CH <sub>2</sub> ) <sub>2</sub> OCH <sub>3</sub>	(oil)
Cl	Cl	(CH <sub>2</sub> ) <sub>3</sub> OCH <sub>3</sub>	(oil)
CF <sub>3</sub>	F	(CH <sub>2</sub> ) <sub>3</sub> OCH <sub>3</sub>	(oil)
Cl	CN	(CH <sub>2</sub> ) <sub>3</sub> OCH <sub>3</sub>	(oil)
CF <sub>3</sub>	CN	(CH <sub>2</sub> ) <sub>3</sub> OCH <sub>3</sub>	(oil)
Cl	CN	(CH <sub>2</sub> ) <sub>4</sub> OCH <sub>3</sub>	(oil)
Cl	CN	(CH <sub>2</sub> ) <sub>3</sub> OC <sub>2</sub> H <sub>5</sub>	(oil)
CF <sub>3</sub>	CN	(CH <sub>2</sub> ) <sub>3</sub> OC <sub>2</sub> H <sub>5</sub>	(oil)
Cl	Cl	(CH <sub>2</sub> ) <sub>2</sub> CN	(oil)
Cl	Cl	(CH <sub>2</sub> ) <sub>3</sub> CN	(oil)
CF <sub>3</sub>	CN	(CH <sub>2</sub> ) <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	(oil)*
CF <sub>3</sub>	CN	(CH <sub>2</sub> ) <sub>2</sub> -3-methylthio-phenyl	(oil)
CF <sub>3</sub>	CN	CH <sub>2</sub> -3-methylsulphonyl-phenyl	(oil)
CF <sub>3</sub>	CN	CH <sub>2</sub> -4-methylsulphonyl-phenyl	(oil)
CF <sub>3</sub>	CN	CH <sub>2</sub> -4-fluorophenyl	(oil)

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	R <sup>3</sup>	R <sup>4</sup>	R <sup>9</sup>	m.p. (°C.)
5	CF <sub>3</sub>	CN	CH <sub>2</sub> -3-pyridyl	(oil)
	CF <sub>3</sub>	CN	CH <sub>2</sub> -4-pyridyl	133-134
10	CF <sub>3</sub>	CN	CH <sub>2</sub> -(2-methylthiazol-4-yl)	(oil)
	CF <sub>3</sub>	CN	CH <sub>2</sub> CH(OCH <sub>3</sub> )CH <sub>2</sub> OCH <sub>3</sub>	(oil)**
15	CF <sub>3</sub>	CN	(CH <sub>2</sub> ) <sub>2</sub> CHOH-4-fluorophenyl	82-86
	CF <sub>3</sub>	CN	(CH <sub>2</sub> ) <sub>2</sub> O-4-methylsulphonylphenyl	(oil)*
20	CF <sub>3</sub>	CN	(CH <sub>2</sub> ) <sub>2</sub> SC <sub>6</sub> H <sub>5</sub>	59-62
	CF <sub>3</sub>	CN	(CH <sub>2</sub> ) <sub>2</sub> S-3-methylsulphonylphenyl	(oil)
25	CF <sub>3</sub>	CN	(CH <sub>2</sub> ) <sub>3</sub> SC <sub>6</sub> H <sub>5</sub>	(oil)

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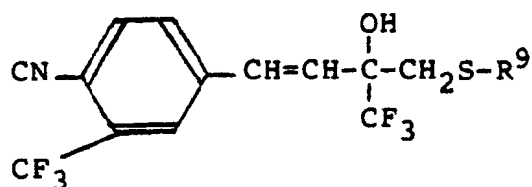
**Example 3**

Aqueous 2N-sodium hydroxide solution (0.75 ml.) was added dropwise to a stirred suspension of 3-hydroxy-3-p-methoxyphenylpropylisothiuronium bromide (0.236 g.) and 4-(4-cyano-3-trifluoromethylphenyl)-1,2-epoxy-2-trifluoromethylbut-trans-3-ene (0.205 g.) in tetrahydrofuran which was maintained at laboratory temperature under an atmosphere of argon, and the mixture was stirred at laboratory temperature for 20 hours and was then poured into saturated aqueous ammonium chloride solution (30 ml.). The mixture was extracted three times with diethyl ether (25 ml. each time) and the combined extracts were washed with saturated aqueous sodium chloride solution (25 ml.), dried over magnesium sulphate and evaporated to dryness. The mixture was purified by flash chromatography on a silica gel (Merck 9385) column using a 40:1 v/v mixture of methylene chloride and ethyl acetate as eluent. There was thus obtained, as an oil, 4-(4-cyano-3-trifluoromethylphenyl)-1-(3-hydroxy-3-p-methoxyphenylpropyl)thio-2-trifluoromethylbut-trans-3-en-2-ol.

The process described above was repeated using the appropriate isothiuronium bromide (or chloride, indicated by an asterisk\* in the table) and the appropriate epoxide as starting materials, and there were thus obtained the compounds described in the following table:-

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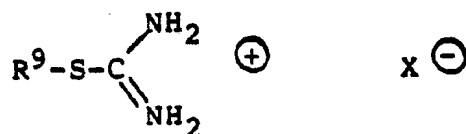
10	R <sup>9</sup>	m.p. (°C)
	(CH <sub>2</sub> ) <sub>3</sub> OH	(oil)
15	(CH <sub>2</sub> ) <sub>3</sub> COCH <sub>3</sub>	(oil)*
	(CH <sub>2</sub> ) <sub>3</sub> COC <sub>6</sub> H <sub>5</sub>	67-70
	(CH <sub>2</sub> ) <sub>3</sub> CO-2-thienyl	(oil)*
20	CH <sub>2</sub> -3-fluorophenyl	85-86
	(CH <sub>2</sub> ) <sub>3</sub> -4-methylthiophenyl	(oil)*
	(CH <sub>2</sub> ) <sub>3</sub> -4-methylsulphonylphenyl	(oil)*
25	(CH <sub>2</sub> ) <sub>3</sub> -4-methoxyphenyl	(oil)
	(CH <sub>2</sub> ) <sub>4</sub> C <sub>6</sub> H <sub>5</sub>	66-69
	(CH <sub>2</sub> ) <sub>2</sub> OC <sub>6</sub> H <sub>5</sub>	83-85
30	(CH <sub>2</sub> ) <sub>3</sub> OC <sub>6</sub> H <sub>5</sub>	63-65
	(CH <sub>2</sub> ) <sub>3</sub> O-4-methylthiophenyl	(oil)*
	(CH <sub>2</sub> ) <sub>2</sub> CHOH-4-methylthiophenyl	(oil)
35	(CH <sub>2</sub> ) <sub>2</sub> CHOH-4-methylsulphonylphenyl	(oil)
	(CH <sub>2</sub> ) <sub>3</sub> CHOHC <sub>6</sub> H <sub>5</sub>	(oil)
	CH <sub>2</sub> CH=CHC <sub>6</sub> H <sub>5</sub> ( <u>trans</u> -)	130-132
40		

There was also obtained by a similar process 4-(3-chloro-4-cyanophenyl)-1-(4-methylsulphonylbenzyl)thio-2-trifluoromethylbut-trans-3-en-2-ol, using 4-methylsulphonylbenzylisothiuronium bromide as starting material.

45 The isothiuronium salts used as starting materials in Examples 2 and 3 were prepared by conventional means from thiourea and the appropriate alkyl halide or tosylate. Those which are novel and which were characterised by melting point are described in the following table:-

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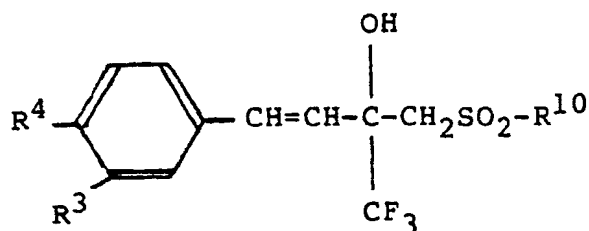
	$\text{R}^9$	$\text{X}^-$	m.p. ( $^{\circ}\text{C}.$ )
10			
15	$(\text{CH}_2)_3\text{C}_6\text{H}_5$	Br	118-119
	$\text{CH}_2$ -3-methylsulphonylphenyl	Cl	199-202
	$\text{CH}_2$ -(2-methylthiazol-4-yl)	Cl	168-170
20	$\text{CH}_2\text{CH}(\text{OCH}_3)\text{CH}_2\text{OCH}_3$	tosylate	105-106
	$(\text{CH}_2)_2$ 0-4-methylsulphonyl-phenyl	Br	165-167
	$(\text{CH}_2)_3\text{COCH}_3$	Cl	139-142
25	$(\text{CH}_2)_3\text{CO}$ -2-thienyl	Cl	112-114
	$(\text{CH}_2)_3$ -4-methylthiophenyl	Cl	118-121
	$(\text{CH}_2)_3$ -4-methylsulphonyl-phenyl	Cl	161-166
30			
	$(\text{CH}_2)_3$ 0-4-methylthiophenyl	Cl	123-126
	$(\text{CH}_2)_2\text{CHOH}$ -4-methylthio-phenyl	Br	188
35			

#### 40 Example 4

A solution of potassium peroxymonosulphate (1.0 g.) in water (10 ml.) was added to a stirred solution of 4-(3,4-dichlorophenyl)-1-[(2-methylthioethyl)thio]-2-trifluoromethylbut-trans-3-en-2-ol (Example 1; 0.1 g.) in methanol (10 ml.) and the mixture was stirred at laboratory temperature for 16 hours, diluted with water (20 ml.) and extracted with ethyl acetate. The extract was washed with saturated aqueous sodium chloride solution, dried over magnesium sulphate and evaporated to dryness under reduced pressure, and the residue was purified by chromatography on a silica gel column using a 1:1 v/v mixture of petroleum ether (b.p. 60-80 $^{\circ}\text{C}.$ ) and ethyl acetate as eluant. There was thus obtained 4-(3,4-dichlorophenyl)-1-[(2-methylsulphonylthio)ethyl]sulphonyl]-2-trifluoromethylbut-trans-3-en-2-ol, m.p. 187 $^{\circ}\text{C}.$

45 The process described above was repeated using the appropriate thio-compound described in Example 1 or 3 above as starting material, and there were thus obtained the compounds described in the following table:-

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R <sup>3</sup>	R <sup>4</sup>	R <sup>10</sup>	m.p. (°C.)
Cl	Cl	(CH <sub>2</sub> ) <sub>2</sub> OCH <sub>3</sub>	(oil)
Cl	Cl	(CH <sub>2</sub> ) <sub>3</sub> OCH <sub>3</sub>	(oil)
CF <sub>3</sub>	CN	(CH <sub>2</sub> ) <sub>3</sub> OCH <sub>3</sub>	(oil)
Cl	Cl	(CH <sub>2</sub> ) <sub>3</sub> SO <sub>2</sub> CH <sub>3</sub>	130
Cl	CN	(CH <sub>2</sub> ) <sub>3</sub> SO <sub>2</sub> CH <sub>3</sub>	90(d)
CF <sub>3</sub>	CN	(CH <sub>2</sub> ) <sub>3</sub> SO <sub>2</sub> CH <sub>3</sub>	140
Cl	Cl	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	(oil)
Cl	Cl	(CH <sub>2</sub> ) <sub>2</sub> -4-fluorophenyl	(oil)
CF <sub>3</sub>	CN	(CH <sub>2</sub> ) <sub>2</sub> -4-methyl-	(oil)
		sulphonylphenyl	
CF <sub>3</sub>	CN	(CH <sub>2</sub> ) <sub>2</sub> SO <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	155-165
CF <sub>3</sub>	CN	(CH <sub>2</sub> ) <sub>2</sub> SO <sub>2</sub> -3-methyl-	
		sulphonylphenyl	72-74

#### Example 5

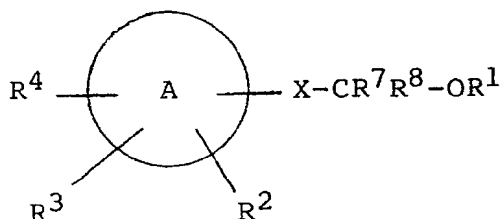
n-Butyl-lithium (1.2 ml. of a 1.6 molar solution in hexane) was added dropwise to a stirred solution of (2-methoxyethoxy)methoxymethyl-tri-n-butylstannane (0.734 g., prepared by a similar process to that described in the Journal of the American Chemical Society, 1978, 100, 1483) in tetrahydrofuran (100 ml.) which was maintained at -78° C. under an atmosphere of argon. The mixture was stirred at -78° C. for 15 minutes, a solution of 1-(3,4-dichlorophenyl)-4,4,4-trifluorobut-1-ene-3-one (0.44 g.) in tetrahydrofuran (10 ml.) was added dropwise and the mixture was stirred for 2 hours at -78° C. Water (1 ml.) was added, the mixture was allowed to warm up to laboratory temperature and diethyl ether (20 ml.) was added. The mixture was washed with saturated aqueous sodium chloride solution, dried over magnesium sulphate and evaporated to dryness. The residue was purified by flash chromatography on a silica gel (Merck 9385) column using a 1:1 v/v mixture of ethyl acetate and petroleum ether (b.p. 60-80° C) as eluent. There was thus obtained as an oil 1-(3,4-dichlorophenyl)-4-(2-methoxyethoxy)-methoxy-3-trifluoromethylbut-trans-1-en-3-ol.

#### Claims

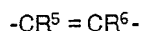
Claims for the following Contracting States: BE, CH, DE, FR, GB, IT, LI, LU, NL, SE



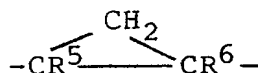
1. A compound of the formula



wherein X has the formula



or



wherein ring A is phenyl, naphthyl, pyridyl, quinolyl or thienyl; wherein  $R^1$  is hydrogen, alkyl or alkanoyl each of up to 6 carbon atoms or aroyl of up to 10 carbon atoms;

wherein  $R^2$ ,  $R^3$  and  $R^4$ , which may be the same or different, each is an electron withdrawing substituent selected from halogeno, nitro, cyano and trifluoromethyl, and alkylthio, alkylsulphinyl and alkylsulphonyl each of up to 6 carbon atoms, or each is hydrogen or alkyl, alkoxy or dialkylamino each of up to 6 carbon atoms, provided that when ring A is phenyl or naphthyl at least one of  $R^2$ ,  $R^3$  and  $R^4$  is an electron-withdrawing substituent;

wherein  $R^5$  and  $R^6$ , which may be the same or different, each is hydrogen, halogeno or alkyl of up to 6 carbon atoms, ;

wherein  $R^7$  is alkyl or halogenoalkyl each of up to 6 carbon atoms;

and wherein  $R^8$  has the formula



wherein Y is straight- or branched-chain alkylene or alkenylene each of up to 6 carbon atoms;

wherein Q is  $-O-$ ,  $-S-$ ,  $-SO-$  or  $-SO_2-$ ;

and wherein  $R^9$  is alkyl of up to 6 carbon atoms which contains one or more substituents selected from halogeno, cyano, hydroxy, amino, hydroxyimino, guanidino, ureido and carbamoyl;

alkoxy, alkylamino, alkylthio, alkylsulphinyl, alkylsulphonyl, alkylcarbamoyl, alkoxyimino, alkanoyl, halogenoalkanoyl, alkanoylamino and alkylsulphonamido each of up to 6 carbon atoms;

alkoxyalkoxy, dialkylamino and dialkylcarbamoyl each of up to 12 carbon atoms;

aryl, aryloxy, arylthio, arylsulphinyl, arylsulphonyl, aryloxyimino and aroyl each of up to 10 carbon atoms;

heterocyclyl, heterocyclylthio, heterocyclylsulphinyl, heterocyclylsulphonyl, heterocycliloxyimino and heterocyclylcarbonyl;

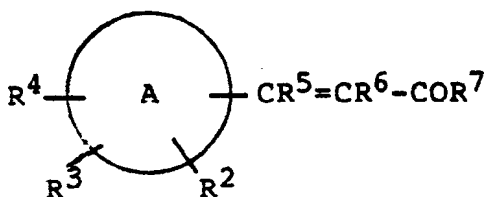
and alkylenedioxy of to 2 to 4 carbon atoms wherein both oxygen atoms are attached to the same carbon atom of  $R^9$ ;

and wherein the heterocyclyl group within each heterocyclyl containing substituent is furyl, thienyl, pyridyl, quinolyl, pyrimidinyl, pyrazinyl, thiazolyl, imidazolyl, triazolyl, purinyl, 1,4-benzodioxanyl, pyrazolopyrimidinyl or acridinyl which is unsubstituted or bears one or more substituents selected from halogeno, trifluoromethyl, hydroxy, mercapto and amino, and alkyl and alkoxy each of up to 6 carbon atoms.

2. A compound as claimed in claim 1 wherein X is  $-CR^5 = CR^6-$ , in the *trans*-configuration, wherein ring A is phenyl, wherein one or two (the same or different) of  $R^2$ ,  $R^3$  and  $R^4$  are fluoro, chloro, cyano, trifluoromethyl or nitro, the others of  $R^2$ ,  $R^3$  and  $R^4$  being hydrogen, wherein  $R^1$ ,  $R^5$  and  $R^6$  are all

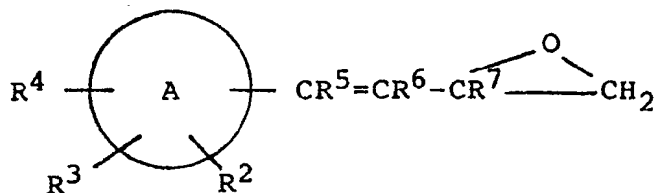
hydrogen, wherein R<sup>7</sup> is trifluoromethyl, pentafluoroethyl, heptafluoropropyl, chloromethyl or dichloromethyl; wherein Q is -S-, -SO- or -SO<sub>2</sub>-, wherein Y is -CH<sub>2</sub>- and wherein R<sup>9</sup> is straight-chain-alkyl of up to 4 carbon atoms which bears one or two substituents selected from chloro, cyano, hydroxy, amino, carbamoyl, methoxy, ethoxy, methylthio, methylsulphonyl, acetyl, acetamido, ureido, dimethylamino, dimethylcarbamoyl, phenyl, fluorophenyl, methylthiophenyl, methylsulphonylphenyl, naphthyl, methoxyphenoxy, phenylthio, methylthiophenylthio, methylsulphonylphenylthio, benzoyl, thenoyl, furyl, pyridyl, pyrazinyl, methylthiazolyl and 1,4-benzodioxanyl; or which bears one such substituent and also three fluorine substituents on the terminal carbon atom; or which bears an ethylenedioxy or trimethylene-1,3-dioxy substituent; or which bears three fluorine substituents on the terminal carbon atom.

3. A compound as claimed in claim 2 wherein ring A is 3,4-dichlorophenyl, 3-chloro-4-cyanophenyl, 4-cyano-3-trifluoromethylphenyl or 4-fluoro-3-trifluoromethylphenyl and wherein R<sup>7</sup> is trifluoromethyl.
4. The compound 1-(3-methoxypropylthio)-, 1-(3-hydroxybutylthio)-, 1-(2-hydroxypropylthio)-, 1-[3,3-(trimethylene-1,3-dioxy)-propylthio]-, 1-(2-furylmethylthio)-, 1-(3-oxobutylthio)- or 1-(3,3-ethylenedioxybutylthio)-4-(4-cyano-3-trifluoromethylphenyl)-2-trifluoromethylbut-trans-3-en-2-ol.
5. The compound 1-(3-hydroxypropylthio)-, 1-(2,3-dihydroxypropylthio)-, 1-(2,3-dimethoxypropylthio)-, 1-benzylthio-, 1-(3-phenylpropylthio)-, 1-m-fluorobenzylthio-, 1-p-fluorobenzylthio-, 1-(3-p-methoxyphenylpropylthio)-, 1-(2-carbamoylethylthio)-, 1-(2-N,N-dimethylcarbamoylethylthio)-, 1-(pyrid-3-ylmethylthio)-, 1-(2-methylthiazol-4-ylmethylthio)-, 1-(3-phenoxypropylthio)-, 1-(4-oxo-4-phenylbutylthio)-, 1-[4-oxo-4-(thien-2-yl)butylthio]-, 1-(3-hydroxy-3-phenylpropylthio)-, 1-(3-p-fluorophenyl-3-hydroxypropylthio)-, 1-(3-hydroxy-3-p-methylthiophenylpropylthio)-, 1-(3-hydroxy-3-p-methylsulphonylphenylpropylthio)- or 1-(3-hydroxy-3-p-methoxyphenylpropylthio)-4-(4-cyano-3-trifluoromethylphenyl)-2-trifluoromethylbut-trans-3-en-2-ol;
6. The compound 1-(2-carbamoylethylthio)-, 1-(p-methylsulphonylbenzylthio)- or 1-(3-methoxypropylthio)-4-(3-chloro-4-cyanophenyl)-2-trifluoromethylbut-trans-3-en-2-ol.
7. The compound 1-(3-methylsulphonylpropylsulphonyl)-4-(3,4-dichlorophenyl)-2-trifluoromethylbut-trans-3-en-2-ol.
8. A process for the manufacture of a compound claimed in any of claims 1 to 7 which comprises:-
  - (a) for the manufacture of an alkene wherein R<sup>1</sup> is hydroxy and X is -CR<sup>5</sup> = CR<sup>5</sup>-, the reaction of a compound of the formula:

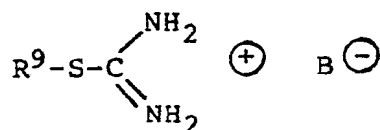


wherein A, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup> and R<sup>7</sup> have the meanings stated in claim 1, 2 or 3 with an organometallic compound of the formula R<sup>8</sup>-M, wherein R<sup>8</sup> has the meaning stated in claim 1 or 2 and M is a metallic group; or

(b) For the manufacture of an alkene wherein R<sup>1</sup> is hydroxy, X is -CR<sup>5</sup>=CR<sup>6</sup>- and Y is -CH<sub>2</sub>-, the reaction of an epoxide of the formula:

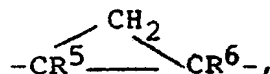


wherein A, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup> and R<sup>7</sup> have the meanings stated above, with a compound of the formula R<sup>9</sup>-Q-H, wherein R<sup>9</sup> and Q have the meanings stated above or, when Q is -S-, with the corresponding isothiuronium salt of the formula

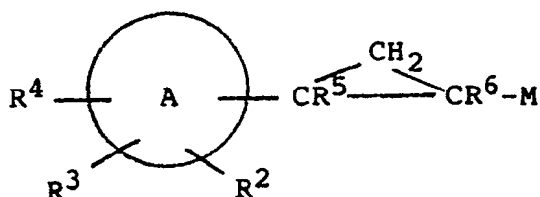


wherein B<sup>⊖</sup> is an anion; or

(c) for the manufacture of a cycloalkylene derivative wherein X is



the reaction of a compound of the formula

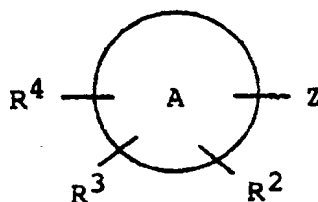


wherein A, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup> and M have the meanings stated above, with a compound of the formula



wherein R<sup>7</sup> and R<sup>8</sup> have the meanings stated above; or

(d) for the manufacture of an alkyne of the invention wherein X is -C≡C-, the reaction of a compound of the formula



wherein A, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> have the meanings stated above and wherein Z is a displaceable group, with a compound of the formula



wherein  $\text{R}^1$ ,  $\text{R}^7$  and  $\text{R}^8$  have the meanings stated above;

whereafter a compound wherein X is  $-\text{C}\equiv\text{C}-$  may be reduced to the corresponding compound wherein X is  $-\text{CH}=\text{CH}-$ ; and whereafter:-

(i) a compound wherein  $\text{R}^9$  bears an amino substituent may be acylated to give the corresponding compound wherein  $\text{R}^9$  bears an alkanoylamino, alkoxycarbonylamino or alkylsulphonamido substituent;

(ii) a compound wherein  $\text{R}^9$  is alkyl substituted by alkanoyl may be reduced to the corresponding compound wherein  $\text{R}^9$  is hydroxyalkyl;

(iii) a compound wherein  $\text{R}^1$  is alkyl may be prepared by the alkylation of the corresponding compound wherein  $\text{R}^1$  is hydrogen.

(iv) a compound wherein  $\text{R}^1$  is alkanoyl or aroyl may be prepared by the acylation of the corresponding compound wherein  $\text{R}^1$  is hydrogen; or

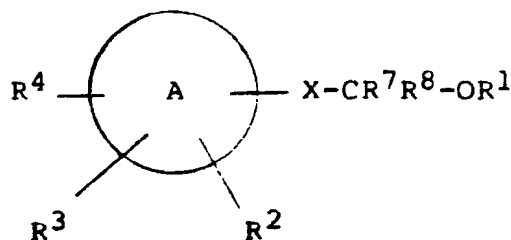
(v) a compound wherein one or more of  $\text{R}^2$ ,  $\text{R}^3$ ,  $\text{R}^4$  and a substituent in  $\text{R}^9$  is alkyl-sulphinyl or alkylsulphonyl, or a substituent in  $\text{R}^9$  is arylsulphinyl, arylsulphonyl, heterocyclisulphinyl or heterocyclisulphonyl, or Q is  $-\text{SO}-$  or  $-\text{SO}_2-$ , may be prepared by the oxidation of the corresponding compound wherein one or more of  $\text{R}^2$ ,  $\text{R}^3$ ,  $\text{R}^4$  and a substituent in  $\text{R}^9$  is alkylthio, arylthio or heterocyclithio, or Q is  $-\text{S}-$ , respectively.

9. A pharmaceutical or veterinary composition which comprises a compound claimed in any of claims 1 to 7 in association with a pharmaceutically-acceptable diluent or carrier.

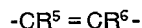
10. The use of a compound, claimed in any of claims 1 to 7, for the manufacture of a medicament for producing an antiandrogenic effect in a warm-blooded animal.

#### Claims for the following Contracting State: AT

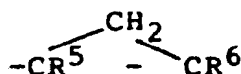
1. A process for the manufacture of a compound of the formula



wherein X has the formula



or



wherein ring A is phenyl, naphthyl, pyridal, quinolyl or thienyl;

wherein  $\text{R}^1$  is hydrogen, alkyl or alkanoyl each of up to 6 carbon atoms or aroyl of up to 10 carbon atoms;

wherein  $\text{R}^2$ ,  $\text{R}^3$  and  $\text{R}^4$ , which may be the same or different, each is an electron withdrawing substituent selected from halogeno, nitro, cyano and trifluoromethyl, and alkylthio, alkylsulphinyl and alkylsulphonyl each of up to 6 carbon atoms, or each is hydrogen or alkyl, alkoxy or dialkylamino each of up to 6

carbon atoms, provided that when ring A is phenyl or naphthyl at least one of  $R^2$ ,  $R^3$  and  $R^4$  is an electron-withdrawing substituent;

wherein  $R^5$  and  $R^6$ , which may be the same or different, each is hydrogen, halogeno or alkyl of up to 6 carbon atoms ;

5 wherein  $R^7$  is alkyl or halogenoalkyl each of up to 6 carbon atoms;

and wherein  $R^8$  has the formula



10 wherein Y is straight- or branched-chain alkylene or alkenylene each of up to 6 carbon atoms;

wherein Q is -O-, -S-, -SO- or -SO<sub>2</sub>-;

and wherein  $R^9$  is alkyl of up to 6 carbon atoms which contains one or more substituents selected from halogeno, cyano, hydroxy, amino, hydroxyimino, guanidino, ureido and carbamoyl;

15 alkoxy, alkylamino, alkylthio, alkylsulphinyl, alkylsulphonyl, alkylcarbamoyl, alkoxyimino, alkanoyl, halogenoalkanoyl, alkanoylamino and alkylsulphonamido each of up to 6 carbon atoms;

alkoxyalkoxy, dialkylamino and dialkylcarbamoyl each of up to 12 carbon atoms;

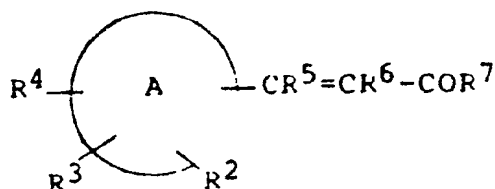
aryl, aryloxy, arylthio, arylsulphinyl, arylsulphonyl, aryloxyimino and aroyl each of up to 10 carbon atoms;

20 heterocyclyl, heterocyclylthio, heterocyclylsulphinyl, heterocyclylsulphonyl, heterocycliloxyimino and heterocyclylcarbonyl;

and alkylenedioxy of to 2 to 4 carbon atoms wherein both oxygen atoms are attached to the same carbon atom of  $R^9$  and wherein the heterocyclyl group within each heterocyclyl containing substituent is furyl, thienyl, pyridyl, quinolyl, pyrimidinyl, pyrazinyl, thiazolyl, imidazolyl, triazolyl, purinyl, 1,4-benzodioxanyl, pyrazolopyrimidinyl or acridinyl which is unsubstituted or bears one or more substituents selected from halogeno, trifluoromethyl, hydroxy, mercapto and amino, and alkyl and alkoxy each of up to 6 carbon atoms; characterised by:-

(a) for the manufacture of an alkene wherein  $R^1$  is hydroxy and X is  $-CR^5=CR^6-$ , the reaction of a compound of the formula:

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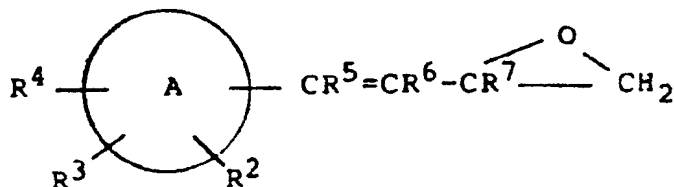


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40 wherein A,  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^5$ ,  $R^6$  and  $R^7$  have the meanings stated above with an organometallic compound of the formula  $R^8-M$ , wherein  $R^8$  has the meaning stated above and M is a metallic group; or

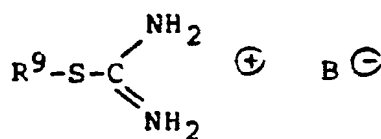
(b) for the manufacture of an alkene wherein  $R^1$  is hydroxy, X is  $-CR^5=CR^6-$  and Y is  $-CH_2-$ , the reaction of an epoxide of the formula:

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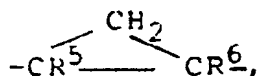
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55 wherein A,  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^5$ ,  $R^6$  and  $R^7$  have the meanings stated above, with a compound of the formula  $R^9-Q-H$ , wherein  $R^9$  and Q have the meanings stated above or, when Q is -S-, with the corresponding isothiuronium salt of the formula

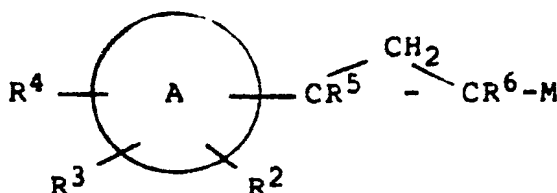


wherein  $\text{B}^-$  is an anion; or

(c) for the manufacture of a cycloalkylene derivative wherein X is



the reaction of a compound of the formula

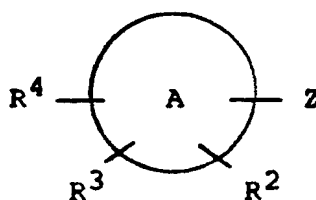


wherein A,  $\text{R}^2$ ,  $\text{R}^3$ ,  $\text{R}^4$ ,  $\text{R}^5$ ,  $\text{R}^6$  and M have the meanings stated above, with a compound of the formula



wherein  $\text{R}^7$  and  $\text{R}^8$  have the meanings stated above; or

(d) for the manufacture of an alkyne of the invention wherein X is  $-\text{C}\equiv\text{C}-$ , the reaction of a compound of the formula



wherein A,  $\text{R}^1$ ,  $\text{R}^2$ ,  $\text{R}^3$  and  $\text{R}^4$  have the meanings stated above and wherein Z is a displaceable group, with a compound of the formula



wherein  $\text{R}^1$ ,  $\text{R}^1$  and  $\text{R}^8$  have the meanings stated above;

whereafter a compound wherein X is  $-\text{C}\equiv\text{C}-$  may be reduced to the corresponding compound wherein X is  $-\text{CH}=\text{CH}-$ ; and whereafter:-

(i) a compound wherein  $\text{R}^9$  bears an amino substituent may be acylated to give the corresponding compound wherein  $\text{R}^9$  bears an alkanoylamino, alkoxycarbonylamino or alkylsulphonamido substituent;

(ii) a compound wherein  $\text{R}^9$  is alkyl substituted by alkanoyl may be reduced to the corresponding compound wherein  $\text{R}^9$  is hydroxyalkyl;

(iii) a compound wherein  $\text{R}^1$  is alkyl may be prepared by the alkylation of the corresponding

compound wherein R<sup>1</sup> is hydrogen.

(iv) a compound wherein R<sup>1</sup> is alkanoyl or aroyl may be prepared by the acylation of the corresponding compound wherein R<sup>1</sup> is hydrogen; or

(v) a compound wherein one or more of R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> and a substituent in R<sup>9</sup> is alkyl-sulphinyl or alkylsulphonyl, or a substituent in R<sup>9</sup> is arylsulphinyl, arylsulphonyl, heterocyclisulphinyl or heterocyclisulphonyl, or Q is -SO- or -SO<sub>2</sub>-, may be prepared by the oxidation of the corresponding compound wherein one or more of R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> and a substituent in R<sup>9</sup> is alkylthio, arylthio or heterocyclithio, or Q is -S-, respectively.

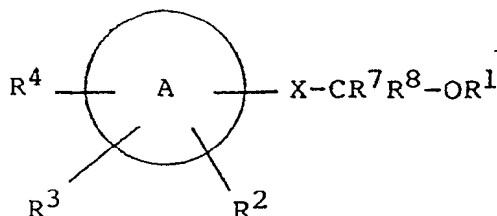
2. A process as claimed in claim 1 wherein in the starting materials X is -CR<sup>5</sup>=CR<sup>6</sup>-, in the trans-configuration, ring A is phenyl, one or two (the same or different) of R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are fluoro, chloro, cyano, trifluoromethyl or nitro, the others of R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> being hydrogen, R<sup>1</sup>, R<sup>5</sup> and R<sup>6</sup> are all hydrogen, R<sup>7</sup> is trifluoromethyl, pentafluoroethyl, heptafluoropropyl, chloromethyl or dichloromethyl; Q is -S-, -SO- or -SO<sub>2</sub>-, Y is -CH<sub>2</sub>- and R<sup>9</sup> is straight-chain-alkyl of up to 4 carbon atoms which bears one or two substituents selected from chloro, cyano, hydroxy, amino, carbamoyl, methoxy, ethoxy, methylthio, methylsulphonyl, acetyl, acetamido, ureido, dimethylamino, dimethylcarbamoyl, phenyl, fluorophenyl, methylthiophenyl, methylsulphonylphenyl, naphthyl, methoxyphenoxy, phenylthio, methylthiophenylthio, methylsulphonylphenylthio, benzoyl, thenoyl, furyl, pyridyl, pyrazinyl, methylthiazolyl and 1,4-benzodioxanyl; or which bears one such substituent and also three fluorine substituents on the terminal carbon atom; or which bears an ethylenedioxy or trimethylene-1,3-dioxy substituent; or which bears three fluorine substituents on the terminal carbon atom.

3. A process as claimed in claim 2 wherein in the starting materials ring A is 3,4-dichlorophenyl, 3-chloro-4-cyanophenyl, 4-cyano-3-trifluoromethylphenyl or 4-fluoro-3-trifluoromethylphenyl and R<sup>7</sup> is trifluoromethyl.

### Revendications

Revendications pour les Etats contractants suivants: BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Composé de formule

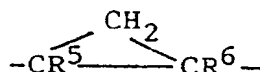


dans laquelle X répond à la formule

-CR<sup>5</sup>=CR<sup>6</sup>-

-C≡C-

ou



où le noyau A est un noyau phényle, naphtyle, pyridyle, quinolyne ou thiényne ; R<sup>1</sup> est l'hydrogène, un groupe alkyle ou un groupe alcanoyl ayant chacun jusqu'à 6 atomes de carbone ou un groupe aroyl ayant jusqu'à 10 atomes de carbone ; R<sup>2</sup>, R<sup>3</sup> et R<sup>4</sup>, qui peuvent être identiques ou différents, représentent chacun un substituant attirant les électrons choisi entre des substituants halogéno, nitro, cyano et trifluorométhyle, et alkylthio, alkylsulfinyle et alkylsulfonyl ayant chacun jusqu'à 6 atomes de carbone, ou bien chacun est l'hydrogène ou un groupe alkyle, alkoxy ou dialkylamino ayant chacun

jusqu'à 6 atomes de carbone, sous réserve que lorsque A est un groupe phényle ou naphthyle, l'un au moins de R<sup>2</sup>, R<sup>3</sup> et R<sup>4</sup> soit un substituant attirant les électrons ;

R<sup>5</sup> et R<sup>6</sup>, qui peuvent être identiques ou différents, représentent chacun l'hydrogène, un radical halogéno ou alkyle ayant jusqu'à 6 atomes de carbone ;

R<sup>7</sup> est un groupe alkyle ou un groupe halogénoalkyle ayant chacun jusqu'à 6 atomes de carbone ;  
et

R<sup>8</sup> répond à la formule

Y-Q-R<sup>9</sup>

dans laquelle Y est un groupe alkylène ou un groupe alcénylène à chaîne droite ou ramifiée ayant chacun jusqu'à 6 atomes de carbone ; Q représente -O-, -S-, -SO- ou -SO<sub>2</sub>-; et R<sup>9</sup> est un groupe alkyle ayant jusqu'à 6 atomes de carbone qui contient un ou plusieurs substituants choisis entre des substituants halogéno, cyano, hydroxy, amino, hydroxyimino, guanidino, uréido et carbamoyle ; alkoxy, alkylamino, alkylthio, alkylsulfinyle, alkylsulfonyle, alkylcarbamoyle, alkoxyimino, alcanoyle, halogénalcanoyle, alcanoylamino et alkylsulfonamido ayant chacun jusqu'à 6 atomes de carbone ; alkoxyalkoxy, dialkylamino et dialkylcarbamoyle ayant chacun jusqu'à 12 atomes de carbone ; aryle, aryloxy, arylthio, arylsulfinyle, arylsulfonyle, aryloxyimino, et aroyle ayant chacun jusqu'à 10 atomes de carbone ; hétérocyclyle, hétérocyclylthio, hétérocyclylsulfinyle, hétérocyclylsulfonyle, hétérocyclyloximino et hétérocyclylcarbonyle ; et alkylènedioxy ayant 2 à 4 atomes de carbone dont les deux atomes d'oxygène sont attachés au même atome de carbone de R<sup>9</sup> ; et le groupe hétérocyclyle dans chaque substituant contenant un groupe hétérocyclyle est un groupe furyle, thiényle, pyridyle, quinolye, pyrimidinyle, pyrazinyle, thiazolye, imidazolyle, triazolyle, purinyle, 1,4-benzodioxannyle, pyrazolopyrimidinyle ou acridinyle qui est non substitué ou qui porte un ou plusieurs des substituants choisis entre des substituants halogéno, trifluorométhyle, hydroxy, mercapto et amino, et alkyle et alkoxy ayant chacun jusqu'à 6 atomes de carbone.

2. Composé suivant la revendication 1, dans lequel X est un groupe -CR<sup>5</sup> = CR<sup>6</sup>-, en configuration trans, le noyau A est un noyau phényle, un ou deux (identiques ou différents) de R<sup>2</sup>, R<sup>3</sup> et R<sup>4</sup> représentent un radical fluoro, chloro, cyano, trifluorométhyle ou nitro, le reste étant de l'hydrogène, R<sup>1</sup>, R<sup>5</sup> et R<sup>6</sup> représentent tous l'hydrogène, R<sup>7</sup> est un groupe trifluorométhyle, pentafluoréthyle, heptafluoropropyle, chlorométhyle ou dichlorométhyle ; Q représente -S-, -SO- ou -SO<sub>2</sub>-, Y est un groupe -CH<sub>2</sub>- et R<sup>9</sup> est un groupe alkyle à chaîne droite ayant jusqu'à quatre atomes de carbone, qui porte un ou deux substituants choisis parmi les substituants, chloro, cyano, hydroxy, amino, carbamoyle, méthoxy, éthoxy, méthylthio, méthylsulfonyle, acétyle, acétamido, uréido, diméthylamino, diméthylcarbamoyle, phényle, fluorophényle, méthylthiophényle, méthylsulfonylphényle, naphthyle, méthoxyphénoxy, phénylthio, méthylthiophénylthio, méthylsulfonylphénylthio, benzoyle, thénoyle, furyle, pyridyle, pyrazinyle, méthylthiazolye et 1,4-benzodioxannyle ; ou qui porte un tel substituant ainsi que trois substituants fluoro sur l'atome terminal de carbone ; ou qui porte un substituant éthylènedioxy ou triméthylène-1,3-dioxy ; ou qui porte trois substituants fluoro sur l'atome terminal de carbone.

3. Composé suivant la revendication 2, dans lequel le noyau A est un noyau 3,4-dichlorophényle, 3-chloro-4-cyanophényle, 4-cyano-3-trifluorométhylphényle ou 4-fluoro-3-trifluorométhylphényle et R<sup>7</sup> est un groupe trifluorométhyle.

4. Le composé 1-(3-méthoxypropylthio)-, 1-(3-hydroxybutylthio)-, 1-(2-hydroxypropylthio)-, 1-[3,3-(triméthylène-1,3-dioxy)-propylthio]-, 1-(2-furylméthylthio)-, 1-(3-oxobutylthio)- ou 1-(3,3-éthylènedioxybutylthio) -4- (4-cyano-3-trifluorométhylphényl)-2-trifluorométhylbut-trans-3-ène-2-ol.

5. Le composé 1-(3-hydroxypropylthio)-, 1-(2,3-dihydroxypropylthio)-, 1-(2,3-diméthoxypropylthio)-, 1-benzylthio-, 1-(3-phénylpropylthio)-, 1-m-fluorobenzylthio, 1-p-fluorobenzylthio-, 1-(3-p-méthoxyphénylpropylthio)-, 1-(2-carbamoyléthylthio)-, 1-(2-N,N-diméthylcarbamoyléthylthio)-, 1-(pyrid-3-ylméthylthio)-, 1-(2-méthylthiazole-4-ylméthylthio)-, 1-(3-phénoxypropylthio)-, 1-(4-oxo-4-phénylbutylthio)-, 1-[4-oxo-4-(thièn-2-yl)butylthio]-, 1-(3-hydroxy-3-phénylpropylthio)-, 1-(3-p-fluorophényl-3-hydroxypropylthio)-, 1-(3-hydroxy-3-p-méthylthiophénylpropylthio)-, 1-(3-hydroxy-3-p-méthylsulfonylphénylpropylthio)- ou 1-(3-hydroxy-3-p-méthoxyphénylpropylthio)-4-(4-cyano-3-trifluorométhylphényl)-2-trifluorométhylbut-trans-3-ène-2-ol.

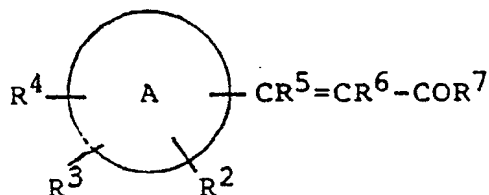


6. Le composé 1-(2-carbamoyléthylthio)-, 1-(p-méthylsulfonylbenzylthio)- ou 1-(3-méthoxypropylthio)-4-(3-chloro-4-cyanophényl)-2-trifluorométhylbut-trans-3-ène-2-ol.

7. Le composé 1-(3-méthylsulfonylpropylsulfonyl)-4-(3,4-dichlorophényl)-2-trifluorométhylbut-trans-3-ène-2-ol.

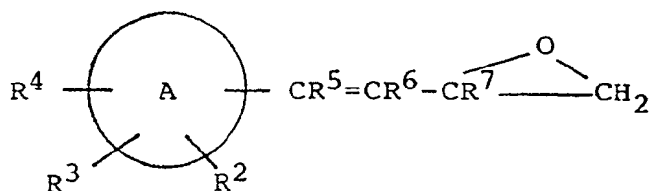
8. Procédé de préparation d'un composé suivant l'une quelconque des revendications 1 à 7, qui comprend :

(a) pour la préparation d'un alcène dans lequel R<sup>1</sup> est un groupe hydroxy et X est un groupe -CR<sup>5</sup>=CR<sup>6</sup>-, la réaction d'un composé de formule :

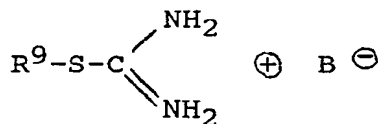


dans laquelle A, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup> et R<sup>7</sup> ont les définitions indiquées dans la revendication 1, 2 ou 3, avec un composé organométallique de formule R<sup>8</sup>-M dans laquelle R<sup>8</sup> a la définition indiquée dans la revendication 1 ou 2 et M est un groupe métallique ; ou bien

(b) pour la préparation d'un alcène dans lequel R<sup>1</sup> est un groupe hydroxy, X est un groupe -CR<sup>5</sup>=CR<sup>6</sup>- et Y est un groupe -CH<sub>2</sub>-, la réaction d'un époxyde de formule :

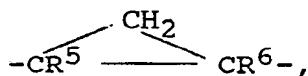


dans laquelle A, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup> et R<sup>7</sup> ont les définitions indiquées ci-dessus, avec un composé de formule R<sup>9</sup>-Q-H, dans laquelle R<sup>9</sup> et Q ont les définitions indiquées ci-dessus ou bien, lorsque Q représente -S-, avec le sel d'isothiuronium de formule

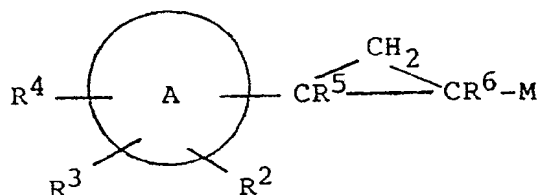


dans laquelle B<sup>⊖</sup> est anion, ou

(c) pour la préparation d'un dérivé cycloalkylénique dans lequel X représente



la réaction d'un composé de formule

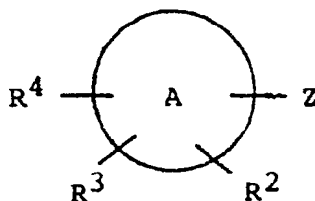


dans laquelle A, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup> et M ont les définitions indiquées ci-dessus, avec un composé de formule



dans laquelle R<sup>7</sup> et R<sup>8</sup> ont les définitions données ci-dessus ; ou bien

(d) pour la préparation d'un alcyne de l'invention, dans laquelle X représente -C≡C-, la réaction d'un composé de formule



dans laquelle A, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> et R<sup>4</sup> ont les définitions indiquées ci-dessus et Z est un groupe déplaçable, avec un composé de formule



dans laquelle R<sup>1</sup>, R<sup>7</sup> et R<sup>8</sup> ont les définitions indiquées ci-dessus ;

après quoi, un composé dans lequel X représente -C≡C- peut être réduit en le composé correspondant dans lequel X est un groupe -CH=CH-, puis :

(i) un composé dans lequel R<sup>9</sup> porte un substituant amino peut être acylé en donnant le composé correspondant dans lequel R<sup>9</sup> porte un substituant alcanoylamino, alkoxycarbonylamino ou alkylsulfonamido ;

(ii) un composé dans lequel R<sup>9</sup> est un groupe alkyle substitué par un radical alcanoyle peut être réduit en le composé correspondant dans lequel R<sup>9</sup> est un groupe hydroxyalkyle ;

(iii) un composé dans lequel R<sup>1</sup> est un groupe alkyle peut être préparé par l'alkylation du composé correspondant dans lequel R<sup>1</sup> est l'hydrogène.

(iv) un composé dans lequel R<sup>1</sup> est un groupe alcanoyle ou aroyle peut être préparé par l'acylation du composé correspondant dans lequel R<sup>1</sup> est l'hydrogène ; ou bien

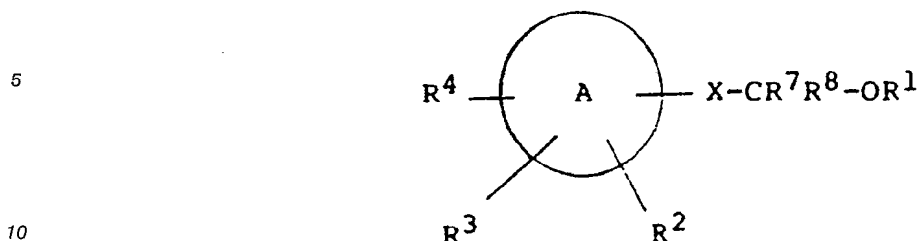
(v) un composé dans lequel un ou plusieurs de R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> et un substituant de R<sup>9</sup> représentent un groupe alkylsulfinyle ou alkylsulfonyle, ou un substituant de R<sup>9</sup> est un groupe arylsulfonyle, arylsulfonyle, hétérocyclysulfinyle ou hétérocyclysulfonyle, ou bien Q est un groupe -SO- ou -SO<sub>2</sub>-, peut être préparé par l'oxydation du composé correspondant dans lequel un ou plusieurs de R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> et un substituant de R<sup>9</sup> représentent un groupe alkylthio, arylthio ou hétérocyclylthio, ou respectivement Q représente -S-.

9. Composition pharmaceutique ou vétérinaire, qui comprend un composé suivant l'une quelconque des revendications 1 à 7 en association avec un diluant ou support acceptable du point de vue pharmaceutique.

10. Utilisation d'un composé suivant l'une quelconque des revendications 1 à 7 pour la préparation d'un médicament destiné à produire un effet anti-androgénique chez un animal à sang chaud.

Revendications pour l'Etat contractant suivant : AT

## 1. Procédé de préparation d'un composé de formule



dans laquelle X répond à la formule

15 -CR<sup>5</sup> = CR<sup>6</sup>-  
-C≡C-  
ou



25 où le noyau A est un noyau phényle, naphtyle, pyridyle, quinolyne ou thiényne ; R<sup>1</sup> est l'hydrogène, un groupe alkyle ou un groupe alcanoyne ayant chacun jusqu'à 6 atomes de carbone ou un groupe aroyle ayant jusqu'à 10 atomes de carbone ; R<sup>2</sup>, R<sup>3</sup> et R<sup>4</sup>, qui peuvent être identiques ou différents, représentent chacun un substituant attirant les électrons choisi entre des substituants halogéno, nitro, cyano et trifluorométhyle, et alkylthio, alkylsulfinyle et alkylsulfonyl ayant chacun jusqu'à 6 atomes de carbone, ou bien chacun est l'hydrogène ou un groupe alkyle, alkoxy ou dialkylamino ayant chacun jusqu'à 6 atomes de carbone, sous réserve que lorsque A est un groupe phényle ou naphtyle, l'un au moins de R<sup>2</sup>, R<sup>3</sup> et R<sup>4</sup> soit un substituant attirant les électrons ;

R<sup>5</sup> et R<sup>6</sup>, qui peuvent être identiques ou différents, représentent chacun l'hydrogène, un radical halogéno ou alkyle ayant jusqu'à 6 atomes de carbone ;

R<sup>7</sup> est un groupe alkyle ou un groupe halogénoalkyle ayant chacun jusqu'à 6 atomes de carbone ;

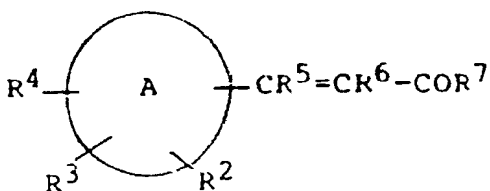
35 et

R<sup>8</sup> répond à la formule

Y-Q-R<sup>9</sup>

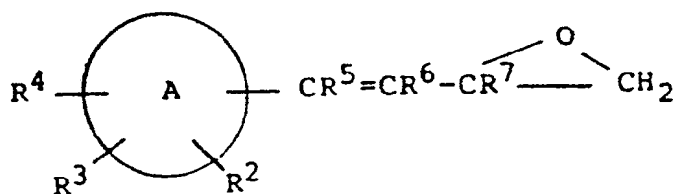
40 dans laquelle Y est un groupe alkylène ou un groupe alcénylène à chaîne droite ou ramifiée ayant chacun jusqu'à 6 atomes de carbone ; Q représente -O-, -S-, -SO- ou -SO<sub>2</sub>- ; et R<sup>9</sup> est un groupe alkyle ayant jusqu'à 6 atomes de carbone qui contient un ou plusieurs substituants choisis entre des substituants halogéno, cyano, hydroxy, amino, hydroxyimino, guanidino, uréido et carbamoyl ; alkoxy, alkylamino, alkylthio, alkylsulfinyle, alkylsulfonyl, alkylcarbamoyl, alkoxyimino, alcanoyl, halogénoalcanoyl, alcanoylamino et alkylsulfonamido ayant chacun jusqu'à 6 atomes de carbone ; alkoxyalkoxy, dialkylamino et dialkylcarbamoyl ayant chacun jusqu'à 12 atomes de carbone ; aryle, aryloxy, arylthio, arylsulfinyle, arylsulfonyl, aryloxyimino, et aroyle ayant chacun jusqu'à 10 atomes de carbone ; hétérocyclyle, hétérocyclylthio, hétérocyclylsulfinyle, hétérocyclylsulfonyl, hétérocyclylloximino et hétérocyclylcarbonyl ; et alkylènedioxy ayant 2 à 4 atomes de carbone dans les deux atomes d'oxygène sont attachés au même atome de carbone de R<sup>9</sup> ; et le groupe hétérocyclyle dans chaque substituant contenant un groupe hétérocyclyle est un groupe furyl, thiényl, pyridyl, quinolyl, pyrimidinyl, pyrazinyl, thiazolyl, imidazolyl, triazolyl, purinyl, 1,4-benzodioxannyl, pyrazolopyrimidinyl ou acridinyl qui est non substitué ou qui porte un ou plusieurs des substituants choisis entre des substituants halogéno, trifluorométhyle, hydroxy, mercapto et amino, et alkyle et alkoxy ayant chacun jusqu'à 6 atomes de carbone, caractérisé par :

55 (a) pour la préparation d'un alcène dans lequel R<sup>1</sup> est un groupe hydroxy et X est un groupe -CR<sup>5</sup> = CR<sup>6</sup>-, la réaction d'un composé de formule :



10 dans laquelle A, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup> et R<sup>7</sup> ont les définitions indiquées ci-dessus, avec un composé organométallique de formule R<sup>8</sup>-M dans laquelle R<sup>8</sup> a la définition indiquée ci-dessus et M est un groupe métallique ; ou bien

15 (b) pour la préparation d'un alcène dans lequel R<sup>1</sup> est un groupe hydroxy, X est un groupe -CR<sup>5</sup>=CR<sup>6</sup>- et Y est un groupe -CH<sub>2</sub>-, la réaction d'un époxyde de formule :



20 dans laquelle A, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup> et R<sup>7</sup> ont les définitions indiquées ci-dessus, avec un composé de formule R<sup>9</sup>-Q-H, dans laquelle R<sup>9</sup> et Q ont les définitions indiquées ci-dessus ou bien, lorsque Q représente -S-, avec le sel d'isothiuronium de formule

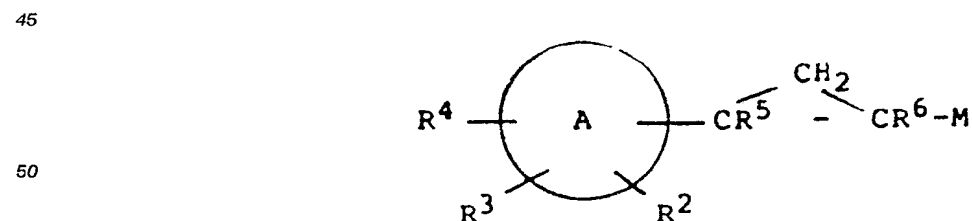


35 dans laquelle B<sup>⊖</sup> est anion ; ou

(c) pour la préparation d'un dérivé cycloalkylénique dans lequel x représente



la réaction d'un composé de formule

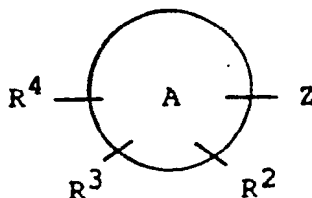


55 dans laquelle A, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup> et M ont les définitions indiquées ci-dessus, avec un composé de formule



dans laquelle  $R^7$  et  $R^8$  ont les définitions données ci-dessus ; ou bien

(d) pour la préparation d'un alcyne de l'invention, dans laquelle X représente  $-C\equiv C-$ , la réaction d'un composé de formule



dans laquelle A,  $R^1$ ,  $R^2$ ,  $R^3$  et  $R^4$  ont les définitions indiquées ci-dessus et Z est un groupe déplaçable, avec un composé de formule



dans laquelle  $R^1$ ,  $R^7$  et  $R^8$  ont les définitions indiquées ci-dessus ;

après quoi, un composé dans lequel X représente  $-C\equiv C-$  peut être réduit en le composé correspondant dans lequel X est un groupe  $-\text{CH}=\text{CH}-$ , puis :

(i) un composé dans lequel  $R^9$  porte un substituant amino peut être acylé en donnant le composé correspondant dans lequel  $R^9$  porte un substituant alcanoylamino, alkoxy-carbonylamino ou alkylsulfonamido ;

(ii) un composé dans lequel  $R^9$  est un groupe alkyle substitué par un radical alcanoyle peut être réduit en le composé correspondant dans lequel  $R^9$  est un groupe hydroxyalkyle ;

(iii) un composé dans lequel  $R^1$  est un groupe alkyle peut être préparé par l'alkylation du composé correspondant dans lequel  $R^1$  est l'hydrogène.

(iv) un composé dans lequel  $R^1$  est un groupe alcanoyle ou aroyle peut être préparé par l'acylation du composé correspondant dans lequel  $R^1$  est l'hydrogène ; ou bien

(v) un composé dans lequel un ou plusieurs de  $R^2$ ,  $R^3$ ,  $R^4$  et un substituant de  $R^9$  représentent un groupe alkylsulfinyle ou alkylsulfonyle, ou un substituant de  $R^9$  est un groupe arylsulfinyle, arylsulfonyle, hétérocyclisulfinyle ou hétérocyclisulfonyle, ou bien Q est un groupe  $-\text{SO}-$  ou  $-\text{SO}_2-$ , peut être préparé par l'oxydation du composé correspondant dans lequel un ou plusieurs de  $R^2$ ,  $R^3$ ,  $R^4$  et un substituant de  $R^9$  représentent un groupe alkylthio, arylthio ou hétérocyclylthio, ou respectivement Q représente  $-\text{S}-$ .

2. Procédé suivant la revendication 1, dans lequel, dans les matières de départ, X est un radical  $-\text{CR}^5 = \text{CR}^6-$ , avec la configuration *trans*, le noyau A est un noyau phényle, un ou deux (identiques ou différents) de  $R^2$ ,  $R^3$  et  $R^4$  sont des radicaux fluoro, chloro, cyano, trifluorométhyle ou nitro, le reste étant de l'hydrogène,  $R^1$ ,  $R^5$  et  $R^6$  sont tous de l'hydrogène,  $R^7$  est un groupe trifluorométhyle, pentafluoréthyle, heptafluoropropyle, chlorométhyle ou dichlorométhyle ; Q représente  $-\text{S}-$ ,  $-\text{SO}-$ , ou  $-\text{SO}_2-$ , Y est un groupe  $-\text{CH}_2-$  et  $R^9$  est un groupe alkyle à chaîne droite ayant jusqu'à 4 atomes de carbone, qui porte un ou deux substituants choisis entre des substituants, chloro, cyano, hydroxy, amino, carbamoyle, méthoxy, éthoxy, méthylthio, méthylsulfonyle, acétyle, acétamido, uréido, diméthylamino, diméthylcarbamoyle, phényle, fluorophényle, méthylthiophényle, méthylsulfonylphényle, naph-tyle, méthoxyphénoxy, phénylthio, méthylthiophénylthio, méthylsulfonylphénylthio, benzoyle, thénoyle, furyle, pyridyle, pyrazinyle, méthylthiazolyle et 1,4-benzodioxannyle ; ou qui porte un tel substituant ainsi que trois substituants fluoro sur l'atome terminal de carbone ; ou qui porte un substituant éthylènedioxy, triméthylène-1,3-dioxy ; ou qui porte trois substituants fluoro sur l'atome terminal de carbone.

3. Procédé suivant la revendication 2, dans lequel le noyau A dans les matières de départ est un noyau de 3,4-dichlorophényle, 3-chloro-4-cyanophényle, 4-cyano-3-trifluorométhylphényle ou 4-fluoro-3-trifluorométhylphényle, et  $R^7$  est un groupe trifluorométhyle.

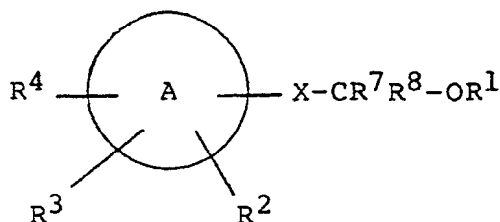
#### Patentansprüche

Patentansprüche für folgende Vertragsstaaten: BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

## 1. Verbindung der Formel

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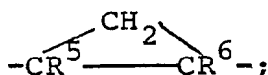
worin

X für eine der folgenden Formel steht:

15

 $-\text{CR}^5 = \text{CR}^6-$ , $-\text{C}\equiv\text{C}-$  oder

20



A für Phenyl, Naphthyl, Pyridyl, Chinolyl oder Thienyl steht;

25

R<sup>1</sup> für Wasserstoff oder Alkyl oder Alkanoyl mit jeweils bis zu 6 Kohlenstoffatomen oder Aroyl mit bis zu 10 Kohlenstoffatomen steht;

R<sup>2</sup>, R<sup>3</sup> und R<sup>4</sup>, welche gleich oder verschieden sein können, jeweils für einen elektronenabziehenden Substituenten, der aus Halogeno, Nitro, Cyano und Trifluoromethyl sowie Alkylthio, Alkylsulfinyl und Alkylsulfonyl mit jeweils bis zu 6 Kohlenstoffatomen ausgewählt ist, oder jeweils für Wasserstoff oder Alkyl, Alkoxy oder Dialkylamino mit jeweils bis zu 6 Kohlenstoffatomen stehen, mit der Maßgabe, daß, wenn der Ring A aus Phenyl oder Naphthyl besteht, mindestens eines der Symbole R<sup>2</sup>, R<sup>3</sup> und R<sup>4</sup> für einen elektronenabziehenden Substituenten steht;

30

R<sup>5</sup> und R<sup>6</sup>, welche gleich oder verschieden sein können, jeweils für Wasserstoff, Halogeno oder Alkyl mit bis zu 6 Kohlenstoffatomen stehen;

35

R<sup>7</sup> für Alkyl oder Halogenoalkyl mit jeweils bis zu 6 Kohlenstoffatomen steht;R<sup>8</sup> für die folgende Formel steht: $-\text{Y}-\text{Q}-\text{R}^9$ ;

40

Y für gerades oder verzweigtes Alkyl oder Alkenyl mit jeweils bis zu 6 Kohlenstoffatomen steht;

Q für  $-\text{O}-$ ,  $-\text{S}-$ ,  $-\text{SO}-$  oder  $-\text{SO}_2-$  steht; und

R<sup>9</sup> für Alkyl mit bis zu 6 Kohlenstoffatomen steht, das einen oder mehrere Substituenten enthält, die ausgewählt sind aus Halogeno, Cyano, Hydroxy, Amino, Hydroxyimino, Guanidino, Ureido und Carbamoyl; Alkoxy, Alkylamino, Alkylthio, Alkylsulfinyl, Alkylsulfonyl, Alkylcarbamoyl, Alkoxyimino, Alkanoyl, Halogenoalkanoyl, Alkanoylamino und Alkylsulfonylamino mit jeweils bis zu 6 Kohlenstoffatomen; Alkoxyalkoxy, Dialkylamino und Dialkylcarbamoyl mit jeweils bis zu 12 Kohlenstoffatomen;

45

Aryl, Aryloxy, Arylthio, Arylsulfinyl, Arylsulfonyl, Aryloxyimino und Aroyl mit jeweils bis zu 10 Kohlenstoffatomen;

50

Heterocyclyl, Heterocyclylthio, Heterocyclylsulfinyl, Heterocyclylsulfonyl, Heterocyclylloxyimino und Heterocyclylcarbonyl; und Alkylendioxy mit 2 bis 4 Kohlenstoffatomen, wobei beide Sauerstoffatome an das gleiche Kohlenstoffatom von R<sup>9</sup> gebunden sind;

wobei die Heterocyclyl-Gruppe innerhalb eines jeden ein Heterocyclyl enthaltenden Substituenten aus Furyl, Thienyl, Pyridyl, Chinolyl, Pyrimidinyl, Pyrazinyl, Thiazolyl, Imidazolyl, Triazolyl, Purinyl, 1,4-Benzodioxanyl, Pyrazolopyrimidinyl oder Acridinyl besteht, das unsubstituiert ist oder einen oder mehreren Substituenten trägt, die ausgewählt sind aus Halogeno, Trifluoromethyl, Hydroxy, Mercapto und Amino sowie Alkyl und Alkoxy mit jeweils bis zu 6 Kohlenstoffatomen.

55

2. Verbindung nach Anspruch 1, worin X für  $-\text{CR}^5 = \text{CR}^6-$  in der trans-Konfiguration steht, der Ring A für

Phenyl steht, eines oder zwei der Symbole  $R^2$ ,  $R^3$  und  $R^4$  für Fluoro, Chloro, Cyano, Trifluoromethyl oder Nitro (im Falle von zwei können sie gleich oder verschieden sein) stehen und die anderen der Symbole  $R^2$ ,  $R^3$  und  $R^4$  für Wasserstoff stehen,  $R^1$ ,  $R^5$  und  $R^6$  jeweils für Wasserstoff stehen,  $R^7$  für Trifluoromethyl, Pentafluoroethyl, Heptafluoropropyl, Chloromethyl oder Dichloromethyl steht; Q für -S-,  
 5 -SO- oder -SO<sub>2</sub>-steht, Y für -CH<sub>2</sub>- steht und  $R^9$  für gerades Alkyl mit bis zu 4 Kohlenstoffatomen steht, welches einen oder zwei Substituenten trägt, die ausgewählt sind aus Chloro, Cyano, Hydroxy, Amino, Carbamoyl, Methoxy, Ethoxy, Methylthio, Methylsulfonyl, Acetyl, Acetamido, Ureido, Dimethylamino, Dimethylcarbamoyl, Phenyl, Fluorophenyl, Methylthiophenyl, Methylsulfonylphenyl, Naphthyl, Methoxyphenoxy, Phenylthio, Methylthiophenylthio, Methylsulfonylphenylthio, Benzoyl, Thenoyl, Furyl, Pyridyl,  
 10 Pyrazinyl, Methylthiazolyl und 1,4-Benzodioxanyl; oder welches einen solchen Substituenten und außerdem drei Fluor-Substituenten am endständigen Kohlenstoffatom trägt; oder welches einen Ethylendioxy oder Trimethylen-1,3-dioxy-Substituenten trägt; oder welches drei Fluor-Substituenten am endständigen Kohlenstoffatom trägt.

15 3. Verbindung nach Anspruch 2, worin der Ring A für 3,4-Dichlorophenyl, 3-Chloro-4-cyanophenyl, 4-Cyano-3-trifluoro-methylphenyl oder 4-Fluoro-3-trifluoromethylphenyl steht und  $R^7$  für Trifluoromethyl steht.

20 4. Die Verbindungen 1-(3-Methoxypropylthio)-, 1-(3-Hydroxybutylthio)-, 1-(2-Hydroxypropylthio)-, 1-[3,3-(Trimethylen-1,3-dioxy)-propylthio]-, 1-(2-Furylmethylthio)-, 1-(3-Oxobutylthio)- und 1-(3,3-Ethylendioxybutylthio)-4-(4-cyano-3-trifluoromethylphenyl)-2-trifluoromethylbut-trans-3-en-2-ol.

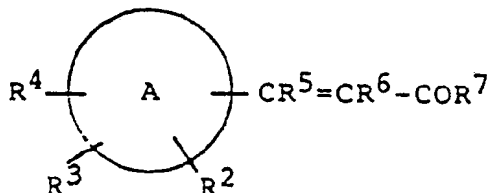
25 5. Die Verbindungen 1-(3-Hydroxypropylthio)-, 1-(2,3-Dihydroxypropylthio)-, 1-(2,3-Dimethoxypropylthio)-, 1-Benzylthio-, 1-(3-Phenylpropylthio)-, 1-m-Fluorobenzylthio-, 1-p-Fluorobenzylthio-, 1-(3-p-Methoxyphenylpropylthio)-, 1-(2-Carbamoylethylthio)-, 1-(2-N,N-Dimethylcarbamoylethylthio)-, 1-Pyrid-3-ylmethylthio-, 1-(2-Methylthiazol-4-ylmethylthio)-, 1-(3-Phenoxypropylthio)-, 1-(4-Oxo-4-phenylbutylthio)-, 1-[4-Oxo-4-(thien-2-yl)butylthio]-, 1-(3-Hydroxy-3-phenylpropylthio)-, 1-(3-p-Fluorophenyl-3-hydroxypropylthio)-, 1-(3-Hydroxy-3-p-methylthiophenylpropylthio)-, 1-(3-Hydroxy-3-p-methylsulfonylphenylpropylthio)- und  
 30 1-(3-Hydroxy-3-p-methoxyphenylpropylthio)-4-(4-cyano-3-trifluoromethylphenyl)-2-trifluoromethylbut-trans-3-en-2-ol.

6. Die Verbindungen 1-(2-Carbamoylethylthio)-, 1-(p-Methylsulfonylbenzylthio)- und 1-(3-Methoxypropylthio)-4-(3-chloro-4-cyanophenyl)-2-trifluoromethylbut-trans-3-en-2-ol.

35 7. Die Verbindung 1-(3-Methylsulfonylpropylsulfonyl)-4-(3,4-dichlorophenyl)-2-trifluoromethylbut-trans-3-en-2-ol.

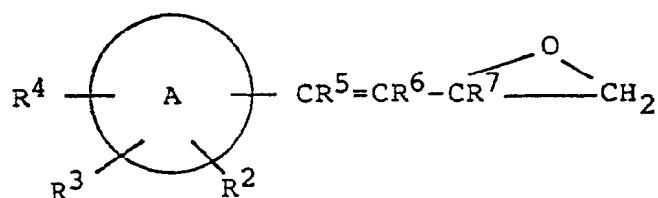
40 8. Verfahren zur Herstellung einer Verbindung nach einem der Ansprüche 1 bis 7, welches folgendes umfaßt:

(a) zur Herstellung eines Alkens, worin  $R^1$  für Hydroxy und X für  $-CR^5 = CR^6-$  steht, Umsetzung einer Verbindung der Formel

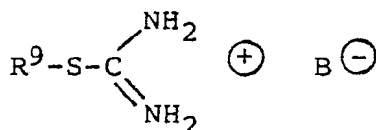


55 worin A,  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^5$ ,  $R^6$  und  $R^7$  die in den Ansprüchen 1, 2 oder 3 angegebenen Bedeutungen besitzen, mit einer Organometallverbindung der Formel  $R^8-M$ , worin  $R^8$  die in Anspruch 1 oder 2 angegebene Bedeutung besitzt und M für eine metallische Gruppe steht; oder

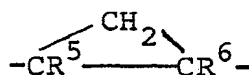
(b) zur Herstellung eines Alkens, worin  $R^1$  für Hydroxy, X für  $-CR^5 = CR^6-$  und Y für -CH<sub>2</sub>- steht, Umsetzung eines Epoxids der Formel



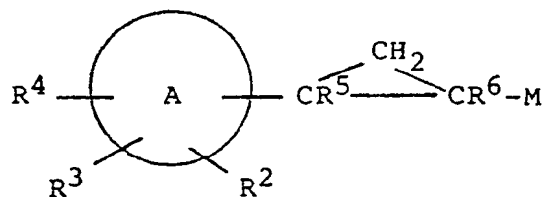
10 worin A, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup> und R<sup>7</sup> die oben angegebenen Bedeutungen besitzen, mit einer Verbindung der Formel R<sup>9</sup>-Q-H, worin R<sup>9</sup> und Q die oben angegebenen Bedeutungen besitzen, oder, wenn Q für -S- steht mit dem entsprechenden Isothiuroniumsalz der Formel



20 worin B<sup>⊖</sup> für ein Anion steht; oder  
(c) zur Herstellung eines Cycloalkylen-Derivats, worin X für



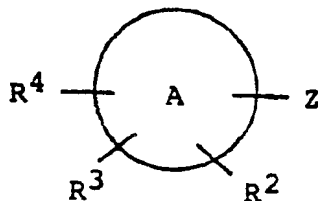
steht, Umsetzung einer Verbindung der Formel



40 worin A, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup> und M die oben angegebenen Bedeutungen besitzen mit einer Verbindung der Formel



45 worin R<sup>7</sup> und R<sup>8</sup> die oben angegebenen Bedeutungen besitzen; oder  
(d) zur Herstellung eines Alkins, worin x für -C≡C- steht, Umsetzung einer Verbindung der Formel



55 worin A, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> und R<sup>4</sup> die oben angegebenen Bedeutungen besitzen und Z für eine ersetzbare Gruppe steht, mit einer Verbindung der Formel





worin  $\text{R}^1$ ,  $\text{R}^7$  und  $\text{R}^8$  die oben angegebenen Bedeutungen besitzen; worauf eine Verbindung, worin X für  $-\text{C}\equiv\text{C}-$  steht, zur entsprechenden Verbindung, worin X für  $-\text{CH}=\text{CH}-$  steht, reduziert werden kann und worauf

(i) eine Verbindung, worin  $\text{R}^9$  einen Amino-Substituenten trägt, acyliert werden kann, um die entsprechende Verbindung herzustellen, worin  $\text{R}^9$  einen Alkanoylamino-, Alkoxy-carbonylamino- oder Alkylsulfonamido-Substituenten trägt;

(ii) eine Verbindung, worin  $\text{R}^9$  für Alkyl, das durch Alkanoyl substituiert ist, steht, zur entsprechenden Verbindung, worin  $\text{R}^9$  für Hydroxyalkyl steht, reduziert werden kann;

(iii) eine Verbindung, worin  $\text{R}^1$  für Alkyl steht, durch Alkylierung der entsprechenden Verbindung, worin  $\text{R}^1$  für Wasserstoff steht, hergestellt werden kann;

(iv) eine Verbindung, worin  $\text{R}^1$  für Alkanoyl oder Aroyl steht, durch Acylierung der entsprechenden Verbindung, worin  $\text{R}^1$  für Wasserstoff steht, hergestellt werden kann; oder

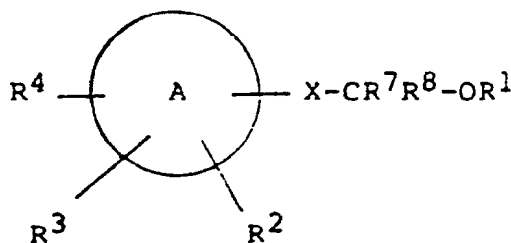
(v) eine Verbindung, worin eines oder mehrere der Symbole  $\text{R}^2$ ,  $\text{R}^3$  und  $\text{R}^4$  oder ein Substituent in  $\text{R}^9$  für Alkylsulfinyl oder Alkylsulfonyl steht oder ein Substituent in  $\text{R}^9$  für Arylsulfinyl, Arylsulfonyl, Heterocyclisulfinyl oder Heterocyclisulfonyl steht oder Q für  $-\text{SO}-$  oder  $-\text{SO}_2-$  steht, hergestellt werden kann durch Oxidation der entsprechenden Verbindung, worin eines oder mehrere Symbole  $\text{R}^2$ ,  $\text{R}^3$  und  $\text{R}^4$  oder ein Substituent in  $\text{R}^9$  für Alkylthio, Arylthio oder Heterocyclylthio bzw. Q für  $-\text{S}-$  steht.

9. Pharmazeutische oder veterinäre Zusammensetzung, welche eine Verbindung nach einem der Ansprüche 1 bis 7 gemeinsam mit einem pharmazeutisch zulässigen Verdünnungs- oder Trägermittel enthält.

10. Die Verwendung einer Verbindung nach einem der Ansprüche 1 bis 7 zur Herstellung eines Medikaments zur Erzielung eines antiandrogenen Effekts bei Warmblütern.

#### Patentansprüche für folgenden Vertragsstaat: AT

1. Verfahren zur Herstellung einer Verbindung der Formel

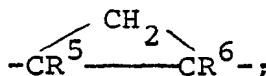


worin

X für eine der folgenden Formel steht:

$-\text{CR}^5 = \text{CR}^6-$ ,

$-\text{C}\equiv\text{C}-$  oder



A für Phenyl, Naphthyl, Pyridyl, Chinolyl oder Thienyl steht;

$\text{R}^1$  für Wasserstoff oder Alkyl oder Alkanoyl mit jeweils bis zu 6 Kohlenstoffatomen oder Aroyl mit bis zu 10 Kohlenstoffatomen steht;

$\text{R}^2$ ,  $\text{R}^3$  und  $\text{R}^4$ , welche gleich oder verschieden sein können, jeweils für einen elektronenabziehenden Substituenten, der aus Halogeno, Nitro, Cyano und Trifluoromethyl sowie Alkylthio, Alkylsulfinyl und

Alkylsulfonyl mit jeweils bis zu 6 Kohlenstoffatomen ausgewählt ist, oder jeweils für Wasserstoff oder Alkyl, Alkoxy oder Dialkylamino mit jeweils bis zu 6 Kohlenstoffatomen stehen, mit der Maßgabe, daß, wenn der Ring A aus Phenyl oder Naphthyl besteht, mindestens eines der Symbole  $R^2$ ,  $R^3$  und  $R^4$  für einen elektronenabziehenden Substituenten steht;

5  $R^5$  und  $R^6$ , welche gleich oder verschieden sein können, jeweils für Wasserstoff, Halogeno oder Alkyl mit bis zu 6 Kohlenstoffatomen stehen;

$R^7$  für Alkyl oder Halogenoalkyl mit jeweils bis zu 6 Kohlenstoffatomen steht;

$R^8$  für die folgende Formel steht:

10  $-Y-Q-R^9$ ;

Y für gerades oder verzweigtes Alkylen oder Alkenylen mit jeweils bis zu 6 Kohlenstoffatomen steht;

Q für  $-O-$ ,  $-S-$ ,  $-SO-$  oder  $-SO_2-$  steht; und

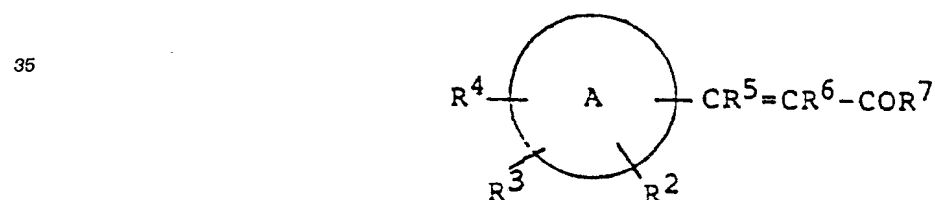
15  $R^9$  für Alkyl mit bis zu 6 Kohlenstoffatomen steht, das einen oder mehrere Substituenten enthält, die ausgewählt sind aus Halogeno, Cyano, Hydroxy, Amino, Hydroxyimino, Guanidino, Ureido und Carbamoyl; Alkoxy, Alkylamino, Alkylthio, Alkylsulfinyl, Alkylsulfonyl, Alkylcarbamoyl, Alkoxyimino, Alkanoyl, Halogenoalkanoyl, Alkanoylamino und Alkylsulfonamido mit jeweils bis zu 6 Kohlenstoffatomen; Alkoxyalkoxy, Dialkylamino und Dialkylcarbamoyl mit jeweils bis zu 12 Kohlenstoffatomen;

20 Aryl, Aryloxy, Arylthio, Arylsulfinyl, Arylsulfonyl, Aryloxyimino und Aroyl mit jeweils bis zu 10 Kohlenstoffatomen;

Heterocyclyl, Heterocyclylthio, Heterocyclylsulfinyl, Heterocyclylsulfonyl, Heterocyclylloxyimino und Heterocyclylcarbonyl; und Alkylendioxy mit 2 bis 4 Kohlenstoffatomen, wobei beide Sauerstoffatome an das gleiche Kohlenstoffatom von  $R^9$  gebunden sind;

25 wobei die Heterocyclyl-Gruppe innerhalb eines jeden ein Heterocyclyl enthaltenden Substituenten aus Furyl, Thieryl, Pyridyl, Chinolyl, Pyrimidinyl, Pyrazinyl, Thiazolyl, Imidazolyl, Triazolyl, Purinyl, 1,4-Benzodioxanyl, Pyrazolopyrimidinyl oder Acridinyl besteht, das unsubstituiert ist oder einen oder mehreren Substituenten trägt, die ausgewählt sind aus Halogeno, Trifluormethyl, Hydroxy, Mercapto und Amino sowie Alkyl und Alkoxy mit jeweils bis zu 6 Kohlenstoffatomen; gekennzeichnet durch

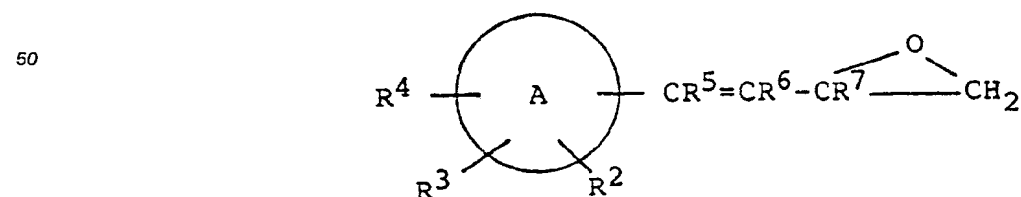
30 (a) zur Herstellung eines Alkens, worin  $R^1$  für Hydroxy und X für  $-CR^5=CR^6-$  steht, Umsetzung einer Verbindung der Formel



worin A,  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^5$ ,  $R^6$  und  $R^7$

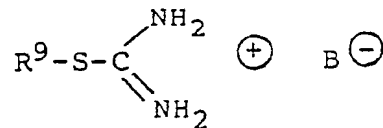
die oben angegebenen Bedeutungen besitzen, mit einer Organometallverbindung der Formel  $R^8-M$ , worin  $R^8$  die oben angegebene Bedeutung besitzt, und M für eine metallische Gruppe steht; oder

45 (b) zur Herstellung eines Alkens, worin  $R^1$  für Hydroxy, X für  $-CR^5=CR^6-$  und Y für  $-CH_2-$  steht, Umsetzung eines Epoxids der Formel



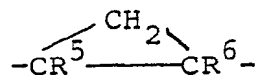
worin A,  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^5$ ,  $R^6$  und  $R^7$  die oben angegebenen Bedeutungen besitzen, mit einer Verbindung der Formel  $R^9-Q-H$ , worin  $R^9$  und Q die oben angegebenen Bedeutungen besitzen,

oder, wenn Q für -S- steht mit dem entsprechenden Isothiuroniumsalz der Formel

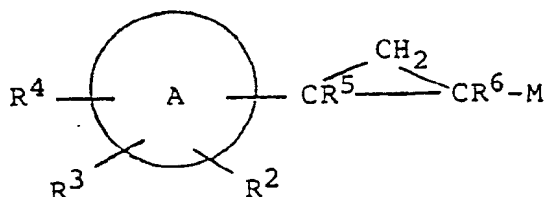


worin B<sup>-</sup> für ein Anion steht; oder

(c) zur Herstellung eines Cycloalkylen-Derivats, worin X für



steht, Umsetzung einer Verbindung der Formel



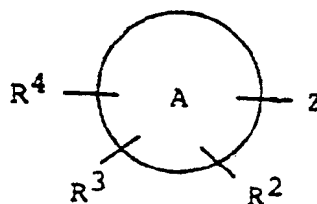
worin A, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup> und M die oben angegebenen Bedeutungen besitzen mit einer Verbindung der Formel



worin R<sup>7</sup> und R<sup>8</sup> die oben angegebenen Bedeutungen besitzen;

oder

(d) zur Herstellung eines Alkins, worin X für -C≡C- steht, Umsetzung einer Verbindung der Formel



worin A, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> und R<sup>4</sup> die oben angegebenen Bedeutungen besitzen und Z für eine ersetzbare Gruppe steht, mit einer Verbindung der Formel



worin R<sup>1</sup>, R<sup>7</sup> und R<sup>8</sup> die oben angegebenen Bedeutungen besitzen; worauf eine Verbindung, worin X für -C≡C- steht, zur entsprechenden Verbindung, worin X für -CH=CH- steht, reduziert werden kann und worauf

(i) eine Verbindung, worin R<sup>9</sup> einen Amino-Substituenten trägt, acyliert werden kann, um die entsprechende Verbindung herzustellen, worin R<sup>9</sup> einen Alkanoylamino-, Alkoxycarbonyl-amino- oder Alkylsulfonamido-Substituenten trägt;

(ii) eine Verbindung, worin R<sup>9</sup> für Alkyl, das durch Alkanoyl substituiert ist, steht, zur entsprechenden Verbindung, worin R<sup>9</sup> für Hydroxyalkyl steht, reduziert werden kann;

(iii) eine Verbindung, worin  $R^1$  für Alkyl steht, durch Alkylierung der entsprechenden Verbindung, worin  $R^1$  für Wasserstoff steht, hergestellt werden kann;

(iv) eine Verbindung, worin  $R^1$  für Alkanoyl oder Aroyl steht, durch Acylierung der entsprechenden Verbindung, worin  $R^1$  für Wasserstoff steht, hergestellt werden kann; oder

(v) eine Verbindung, worin eines oder mehrere der Symbole  $R^2$ ,  $R^3$  und  $R^4$  oder ein Substituent in  $R^9$  für Alkylsulfinyl oder Alkylsulfonyl steht oder ein Substituent in  $R^9$  für Arylsulfinyl, Arylsulfonyl, Heterocyclisulfinyl oder Heterocyclisulfonyl steht oder Q für -SO- oder -SO<sub>2</sub>- steht, hergestellt werden kann durch Oxidation der entsprechenden Verbindung, worin eines oder mehrere Symbole  $R^2$ ,  $R^3$  und  $R^4$  oder ein Substituent in  $R^9$  für Alkylthio, Arylthio oder Heterocyclylthio bzw. Q für -S- steht.

2. Verfahren nach Anspruch 1, bei welchem in den Ausgangsmaterialien X für -CR<sup>5</sup>=CR<sup>6</sup>- in der trans-Konfiguration steht, der Ring A für Phenyl steht, eines oder zwei der Symbole  $R^2$ ,  $R^3$  und  $R^4$  für Fluoro, Chloro, Cyano, Trifluoromethyl oder Nitro (im Falle von zwei können sie gleich oder verschieden sein) stehen und die anderen der Symbole  $R^2$ ,  $R^3$  und  $R^4$  für Wasserstoff stehen,  $R^1$ ,  $R^5$  und  $R^6$  jeweils für Wasserstoff stehen,  $R^7$  für Trifluoromethyl, Pentafluoroethyl, Heptafluoropropyl, Chloromethyl oder Dichloromethyl steht;

Q für -S-, -SO- oder -SO<sub>2</sub>- steht, Y für -CH<sub>2</sub>- steht und  $R^9$  für gerades Alkyl mit bis zu 4 Kohlenstoffatomen steht, das einen oder zwei Substituenten trägt, die ausgewählt sind aus Chloro, Cyano, Hydroxy, Amino, Carbamoyl, Methoxy, Ethoxy, Methylthio, Methylsulfonyl, Acetyl, Acetamido, Ureido, Dimethylamino, Dimethylcarbamoyl, Phenyl, Fluorophenyl, Methylthiophenyl, Methylsulfonylphenyl, Naphthyl, Methoxyphenoxy, Phenylthio, Methylthiophenylthio, Methylsulfonylphenylthio, Benzoyl, Thenoyl, Furyl, Pyridyl, Pyrazinyl, Methylthiazolyl und 1,4-Benzodioxanyl; oder welches einen solchen Substituenten und außerdem drei Fluor-Substituenten am endständigen Kohlenstoffatom trägt; oder welches einen Ethylendioxy oder Trimethylen-1,3-dioxy-Substituenten trägt; oder welches drei Fluor-Substituenten am endständigen Kohlenstoffatom trägt.

3. Verfahren nach Anspruch 2, bei welchem in den Ausgangsmaterialien der Ring A für 3,4-Dichlorophenyl, 3-Chloro-4-cyanophenyl, 4-Cyano-3-trifluoromethylphenyl oder 4-Fluoro-3-trifluoromethylphenyl steht und  $R^7$  für Trifluoromethyl steht.